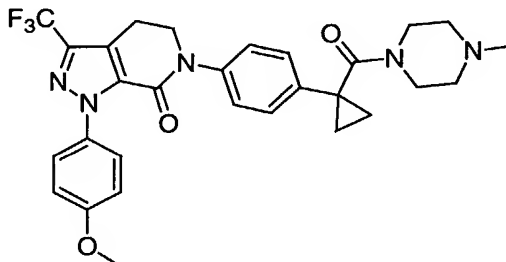


1-(4-methoxyphenyl)-6-(4-{1-[(4-methyl-1-piperazinyl)carbonyl]cyclopropyl}phenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



5

Following a procedure analogous to that used for the preparation of Example 10, but using 4-methylpiperazine, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run).

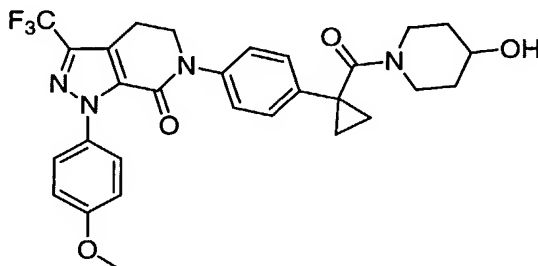
10 LC/MS(ESI⁺) 554.6 (M+H)⁺, t_R = 4.49 min. HRMS C₂₉H₃₁O₃F₃N₅ (M+H)⁺ 554.2384 calcd for 554.2379. ¹H NMR (acetone-d₆) δ 7.50 (d, J = 8.8 Hz, 2H), 7.30 (AA'BB', J = 8.4 Hz, 4H), 6.97 (d, J = 9.1 Hz, 2H), 4.17 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.16 (t, J = 6.4 Hz, 2H), 2.85 (s, 3H), 1.39 (m, 2H), 1.20 (m, 2H) ppm.

15

Example 13

6-{4-[1-(4-hydroxypiperidine-1-carbonyl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one

20



Following a procedure analogous to that used for the preparation of Example 10, but using morpholine, the title compound was prepared. The product was purified by RP-prep

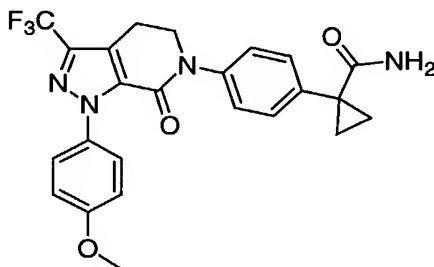
25

LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS(ESI⁺) 555.4 (M+H)⁺, t_R = 5.50 min. HRMS C₂₉H₃₀O₄F₃N₄ (M+H)⁺ 555.2241 calcd for 555.2219.

5

Example 14

1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl}cyclopropanecarboxamide

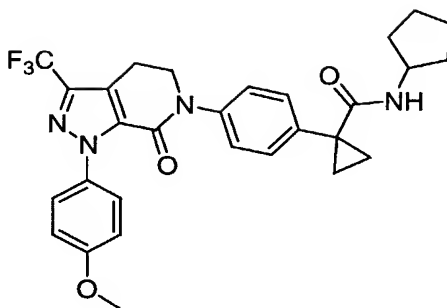


10 Following a procedure analogous to that used for the preparation of Example 10, but using concentrated NH₄OH as the amine source and THF as solvent, the title compound was prepared. The product was purified by prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS(ESI⁺) 471.6 (M+H)⁺, t_R =
15 2.56 min (10-90% CH₃CN/H₂O in a 10-min run). ¹H NMR (acetone-*d*₆) δ 7.50 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.18 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 3.17 (t, *J* = 6.6 Hz, 2H), 1.40 (m, 2H), 0.96 (m, 2H) ppm. ¹⁹F NMR
20 (acetone-*d*₆) δ -77.14 ppm.

Example 15

1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl}cyclopropanecarboxylic acid cyclopentylamide

25

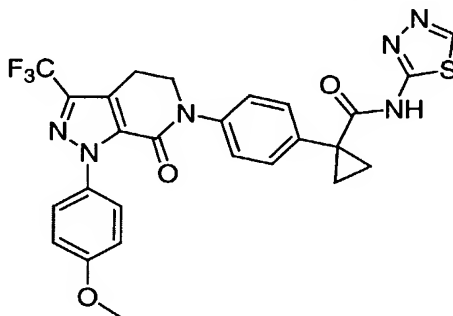


Following a procedure analogous to that used for the preparation of Example 10, but using cyclopentylamine, the title compound was prepared. The product was purified by
 5 RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run).

LC/MS(ESI⁺) 539.4 (M+H)⁺, t_R = 6.65 min. ¹H NMR (acetone-
 d₆) δ 7.51 (d, J = 8.8 Hz, 2H), 7.37 (m, 4H), 6.99 (d, J =
 8.8 Hz, 2H), 4.16 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 4.05
 (m, 1H), 3.16 (t, J = 6.2 Hz, 2H), 1.79 (m, 2H), 1.45 (m,
 10 4H), 1.22 (m, 2H), 1.39 (m, 2H), 0.92 (m, 2H) ppm.

Example 16

**1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-
 1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl}-
 15 N-(1,3,4-thiadiazol-2-yl)cyclopropanecarboxamide**



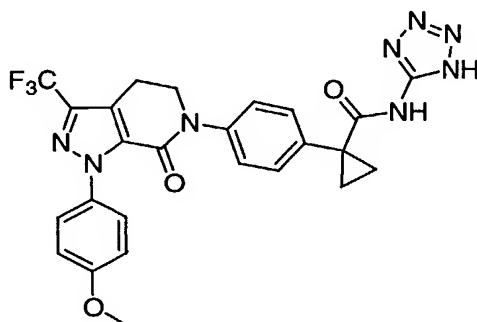
Following a procedure analogous to that used for the preparation of Example 10, but using 2-aminothiadiazole, the title compound was prepared. The product was purified
 20 by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run).

LC/MS(ESI⁺) 555.4 (M+H)⁺, t_R = 6.17 min. ¹H NMR (acetone-
 d₆) δ 8.96 (s, 1H), 7.54 (m, 4H), 7.43 (d, J = 8.4 Hz, 2H),
 6.98 (d, J = 8.9 Hz, 2H), 4.22 (t, J = 6.6 Hz, 2H), 3.84

(s, 3H), 3.16 (t, J = 6.2 Hz, 2H), 1.67 (m, 2H), 1.31 (m, 2H) ppm.

Example 17

5 **1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-
1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl}-
N-(1H-tetrazol-5-yl)cyclopropanecarboxamide**

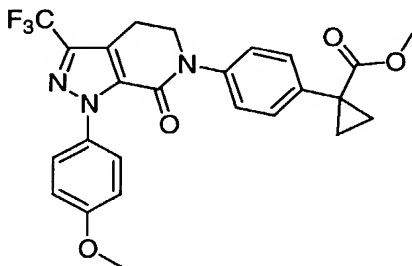


Following a procedure analogous to that used for the
10 preparation of Example 10, but using 5-amino-1H-tetrazole,
the title compound was prepared. The product was purified
by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run).

LC/MS(ESI⁺) 539.6 (M+H), t_R = 5.86 min. ¹H NMR (acetone-*d*₆)
δ 7.53 (m, 4H), 7.39 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 9.1
15 Hz, 2H), 4.20 (t, J = 6.6 Hz, 2H), 3.84 (s, 3H), 3.18 (t, J
= 6.6 Hz, 2H), 1.68 (m, 2H), 1.29 (m, 2H) ppm.

Example 18

20 **methyl 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-
1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-
yl]phenyl}cyclopropanecarboxylate**



The product from part D in Example 1 (mg, mmol) was stirred
in anhydrous MeOH (5 mL) at RT. Catalytic amount of conc.

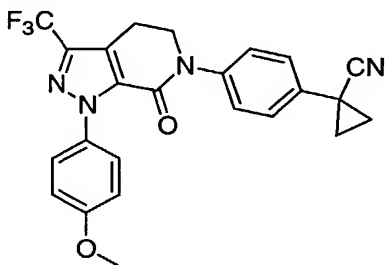
HCl was added. The resulting solution was stirred at RT overnight. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS(ESI⁺) 486.6 (M+H)⁺, t_R = 2.98 min (10-90% CH₃CN/H₂O in a 4-min run). ¹H NMR

(acetone-*d*₆) δ 7.50 (d, *J* = 8.8 Hz, 2H), 7.35 (AA'BB', *J* = 8.8 Hz, 4H), 6.97 (d, *J* = 9.1 Hz, 2H), 4.18 (t, *J* = 6.6 Hz, 2H), 3.82 (s, 3H), 3.55 (s, 3H), 3.17 (t, *J* = 6.4 Hz, 2H), 1.49 (m, 2H), 1.16 (m, 2H) ppm.

10

Example 19

1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropanecarbonitrile

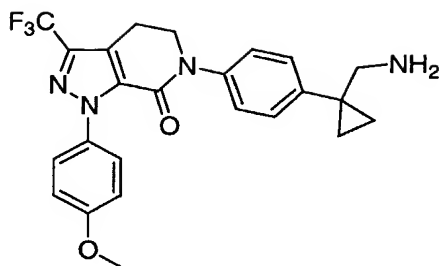


The product from Example 14 (22 mg, 0.047 mmol) was stirred in DMF (0.3 mL) at RT in a capped vial. SOCl₂ (0.05 mL) was added. The mixture was stirred at RT for 1.5 h. LC-MS showed completion of the reaction. Prep LC-MS purification (35-98% CH₃CN in H₂O) provided the title compound (15 mg, yield, 71%). LC/MS(ESI⁺) 453.4 (M+H)⁺, t_R = 5.24 min. ¹H NMR (acetone-*d*₆) δ 7.50 (d, *J* = 9.2 Hz, 2H), 7.39 (m, 4H), 6.97 (d, *J* = 8.8 Hz, 2H), 4.18 (t, *J* = 6.6 Hz, 2H), 3.84 (s, 3H), 3.17 (t, *J* = 6.6 Hz, 2H), 1.71 (m, 2H), 1.48 (m, 2H) ppm. ¹⁹F NMR (acetone-*d*₆) δ -77.16 ppm.

25

Example 20

6-{4-[1-(aminomethyl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



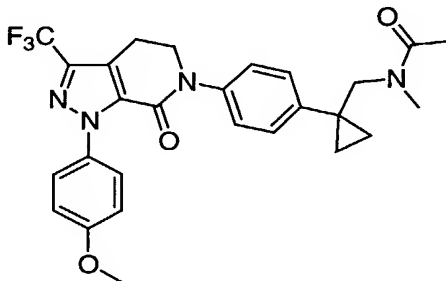
Part A. The product from part E in Example 1 (24 mg, 0.052 mmol) was stirred in CH_2Cl_2 (1 mL) at 0°C under N_2 . Et_3N (11 μL , 1.5 eq) was added followed by the dropwise addition
 5 of MsCl (4.5 μL , 1.1 eq). The mixture was stirred at 0°C for 1 h. TLC showed completion of the reaction. Sat'd NH_4Cl was added. The mixture was extracted with EtOAc . The organic layer was washed with H_2O and brine, dried over Na_2SO_4 , filtered, and concentrated to dryness. The residue
 10 was dissolved in DMF (1 mL). NaN_3 (50 mg, mmol) was added. The mixture was stirred at RT under N_2 overnight. LC-MS showed the azide as the major component in the mixture. Sat'd NH_4Cl was then added. The mixture was extracted with EtOAc . And the organic layer was washed with H_2O and
 15 brine, dried over Na_2SO_4 , filtered, and concentrated to dryness to give crude 6-{4-[1-azidomethylcyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one. LC/MS(ESI^+) 483.4 ($\text{M}+\text{H}^+$), $t_R = 3.06$ min
 20 (10-90% CH_3CN in H_2O in a 4-min run).

Part B. The product from part A (18 mg) and PPh_3 (38 mg) were stirred in THF (1.5 mL) at RT for 20 min. H_2O (0.3 mL) was added, and the mixture was stirred at 30°C for 2 h.
 25 The solvents were evaporated. The residue was purified by prep LC-MS (5-98% CH_3CN in H_2O) to give pure 6-{4-[1-(aminomethyl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-

c]pyridin-7-one (7 mg, yield: 29%). LC/MS (ESI⁺) 457.4 (M+H)⁺.

Example 21

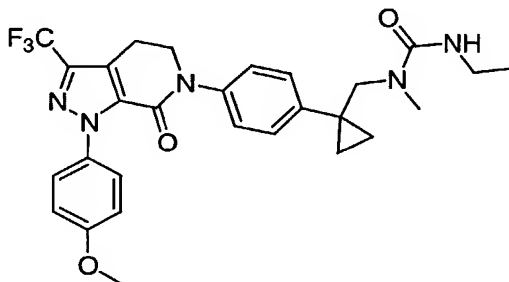
5 ***N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)methyl]-*N*-methylacetamide**



The product of Example 1 (40 mg, 0.084 mmol) was stirred in
 10 CH₂Cl₂ (1 mL) in a capped vial at RT. Et₃N (4 drops) was added followed by addition of acetyl chloride (2 drops). The resulting mixture was stirred at RT for 10 min. LC-MS showed completion of the reaction. After evaporation of the solvents, the residue was dissolved in MeOH (1 mL) and
 15 purified by prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run) to afford pure *N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)methyl]-*N*-methylacetamide (35 mg, yield: 80.3%). LC/MS (ESI⁺) 513.4 (M+H)⁺, *t*_R = 6.08
 20 min. HRMS C₂₇H₂₈O₃F₃N₄ (M+H)⁺ 513.2120 calcd for 513.2113.
¹H NMR (acetone-*d*₆) δ 7.49 (d, *J* = 9.1 Hz, 2H), 7.33 (m, 4H), 6.97 (d, *J* = 9.0 Hz, 2H), 4.15 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 3.58 (s, 1H), 3.49 (s, 1H), 3.16 (t, *J* = 6.6 Hz, 2H), 2.91, 2.80 (2 x s, 3H), 1.89, 1.50 (2 x s, 3H),
 25 0.87 (m, 2H), 0.78 (m, 2H) ppm.

Example 22

***N'*-ethyl-*N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)methyl]-*N*-methylurea**



5

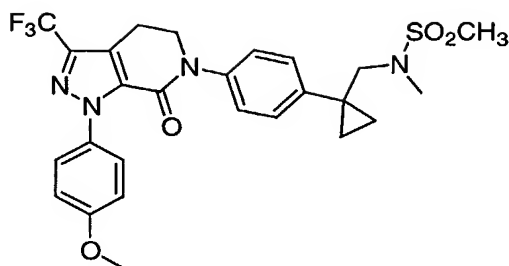
The product of Example 1 (20 mg, 0.042 mmol) was stirred in CH₂Cl₂ (1 mL) in a capped vial at RT. Et₃N (4 drops) was added followed by addition of ethyl isocyanide (2 drops). The resulting mixture was stirred at RT for 2 h. LC-MS showed completion of the reaction. After evaporation of the solvents, the residue was dissolved in MeOH (1 mL), and purified by prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run) to afford pure *N'*-ethyl-*N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)methyl]-*N*-methylurea (16 mg, yield: 70%). HRMS C₂₈H₃₁O₃F₃N₅ 542.2370 (M+H), calcd for 542.2380. ¹H NMR (acetone-*d*₆) δ 7.49 (d, *J* = 9.2 Hz, 2H), 7.30 (AA'BB', *J* = 8.4 Hz, 4H), 6.97 (d, *J* = 8.8 Hz, 2H), 4.14 (t, *J* = 6.3 Hz, 2H), 3.82 (s, 3H), 3.51 (s, 2H), 3.16 (t, *J* = 6.4 Hz, 2H), 3.02 (q, *J* = 7.0 Hz, 2H), 2.70 (s, 3H), 0.92 (t, *J* = 7.0 Hz, 3H), 0.86 (m, 2H), 0.76 (m, 2H) ppm.

20

Example 23

***N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)methyl]-*N*-methylmethanesulfonamide**

25

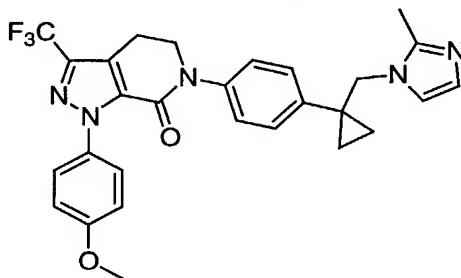


The product of Example 1 (20 mg, 0.042 mmol) was stirred in CH_2Cl_2 (1 mL) in a capped vial at RT. Pyridine (4 drops) was added followed by two drops of methanesulfonyl chloride. The resulting mixture was stirred for 20 min. LC-MS showed completion of the reaction. After evaporation of the solvents, the residue was dissolved in MeOH (1 mL), and purified by prep LC-MS (5-98% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ in a 10-min run) to afford pure *N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-
 10 c]pyridin-6-yl]phenyl}cyclopropyl)methyl]-*N*-methylmethanesulfonamide (16 mg, yield: 69%). LC/MS(ESI⁺) 549.4 (M+H)⁺, t_R = 6.40 min.

15

Example 24

1-(4-methoxyphenyl)-6-{4-[1-(2-methylimidazol-1-ylmethyl)cyclopropyl]phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



20 Part A. The product of part E in Example 1 (0.45 g, 0.98 mmol) was stirred in CH_2Cl_2 (10 mL) at 0°C under N_2 . PPh_3 (0.52 g, 2.0 eq) was added, followed by the addition of CBr_4 (0.33 g, 1.0 eq). The resulting mixture was stirred at 0°C for 30 min. LC-MS showed completion of the
 25 reaction. The mixture was extracted with EtOAc. The

organic layer was washed with H₂O and brine, dried over MgSO₄, filtered, and concentrated to dryness. It was used directly in the next step without purification.

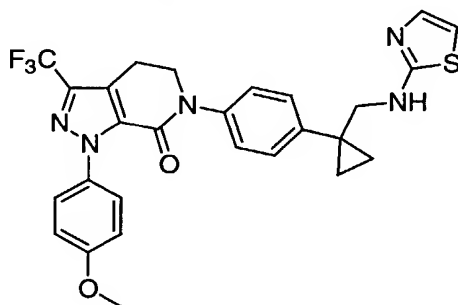
LC/MS(ESI⁺) 520.4, 522.4 (M+H)⁺.

5

Part B. The product of Part A (0.20 g, 0.38 mmol), 2-methylimidazole (0.10 g, 1.22 mmol), and K₂CO₃ (0.25 g, 3.62 mmol) were stirred in DMF (0.4 mL) at RT under N₂. The mixture was heated at 85-90°C for 30 min. LC-MS showed
 10 completion of the reaction. After cooling to RT, H₂O was added. The mixture was purified by prep LC-MS (35-98% CH₃CN in H₂O) to give pure 1-(4-methoxyphenyl)-6-{4-[1-(2-methylimidazol-1-ylmethyl)cyclopropyl]phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-
 15 7-one (53 mg, yield: 27%). LC/MS(ESI⁺) 522.4 (M+H)⁺. ¹H NMR (acetone-*d*₆) δ 7.53 (m, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.39 (m, 1H), 7.25 (AA'BB', *J* = 8.4 Hz, 4H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.38 (s, 2H), 4.15 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 3.14 (t, *J* = 6.6 Hz, 2H), 2.10 (s, 3H), 1.26 (t, *J* = 5.5 Hz, 2H), 1.02 (t, *J* = 5.5 Hz, 2H) ppm.
 20

Example 25

1-(4-methoxyphenyl)-6-{4-[1-(thiazol-2-ylaminomethyl)-cyclopropyl]phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one
 25

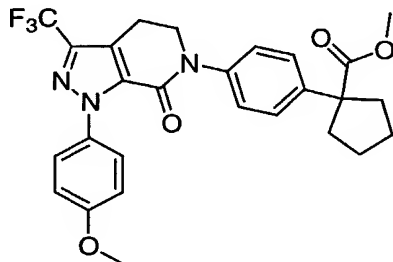


Following a procedure analogous to that of Example 24, the title compound was prepared by using 2-aminothiazole. The

product was purified by RP-prep LC-MS (35-98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 540.6 (M+H)⁺, t_R = 3.37 min.

Example 26

5 **methyl 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl}cyclopentanecarboxylate**



Part A. 1-Phenyl-cyclopentylcarboxylic acid (3.0 g, 15.8
10 mmol) was stirred in HOAc (10 mL) at RT under N₂. I₂ (4.01 g, 15.8 mmol) was added followed by the addition of NaIO₃ (0.78 g, 3.94 mmol) and conc. H₂SO₄ (0.3 mL). The resulting mixture was stirred at 70°C for 3 days. The cooled mixture was poured into H₂O, and extracted with EtOAc. The organic
15 layer was washed with sodium thiosulfate and brine, dried over MgSO₄, filtered, and concentrated to dryness to yield 4-iodophenylcyclopentylcarboxylic acid (4.45 g, yield: 89%). LC/MS(ESI⁺) 317.6 (M+H)⁺.

20 Part B. The product from part A (1.08 g, 3.43 mmol) and 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (0.82 g, 2.64 mmol) were stirred in DMSO (3 mL) under N₂. K₂CO₃ (1.09 g, 7.90 mmol, 3.0 eq) was added followed by the addition of 1,10-
25 phenanthroline (96 mg, 20 mol%) and CuI (100 mg, 20mol%). The resulting mixture was stirred at 130°C for 5h. LC-MS showed completion of the reaction. It was acidified with 1N HCl, and extracted with EtOAc (2x). The organic layer was washed with H₂O, brine, dried over MgSO₄, filtered, and
30 concentrated to afford 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-

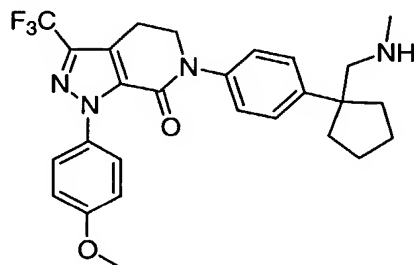
(trifluoromethyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl}cyclopentanecarboxylic acid (1.30 g, yield: 99%). LC/MS(ESI⁺) 500.6 (M+H)⁺.

5 Part C. The product of part B (40 mg, 0.080 mmol) was dissolved in MeOH (5 mL), and conc. HCl (0.5 mL) was added. The resulting mixture was stirred at 60°C overnight. After cooling, the mixture was purified by prep LC-MS (35-98% CH₃CN in H₂O in a 10-min run) to afford methyl
10 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl}cyclopentane carboxylate (32 mg, yield: 78%).
LC/MS(ESI⁺) 514.6 (M+H)⁺, t_R = 6.09 min. ¹H NMR (CDCl₃) δ
7.45 (d, J = 8.8 Hz, 2H), 7.30 (AA'BB', J = 8.6 Hz, 4H),
15 6.92 (d, J = 9.0 Hz, 2H), 4.13 (t, J = 6.8 Hz, 2H), 3.81 (s, 3H), 3.39 (s, 3H), 3.15 (t, J = 6.6 Hz, 2H), 2.65-2.58 (m, 2H), 1.89-1.82 (m, 2H), 1.73-1.69 (m, 4H), 1.58 (m, 2H) ppm.

20

Example 27

1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopentyl}phenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



25

Part A. The product from part B of Example 26 (1.46 g, 2.93 mmol) was stirred in THF (10 mL) at 0°C under N₂. Et₃N (0.62 mL, 4.40 mmol, 1.5 eq) was added followed by dropwise addition of ClCO₂Et (0.31 mL, 3.24 mmol, 1.1 eq). The
30 reaction mixture was then stirred at 0°C for 1 h. TLC

showed completion of the reaction. The mixture was filtered, and rinsed with anhydrous THF. The THF filtrate (ca. 20 mL) was stirred at 0°C under N₂. MeOH (5 mL) was added followed by the addition of NaBH₄ (1.03 g, 27.10 mmol, 9.3 eq). The resulting mixture was stirred at 0°C for 40 min. Analytical LC-MS showed completion of the reaction. Sat'd Na₂SO₄ was then added. The mixture was extracted with EtOAc (2x). The organic layer was washed with H₂O (2x) and brine (2x), dried over Na₂SO₄, filtered, and concentrated to dryness to give 6-{4-[1-(hydroxymethyl)cyclopentyl]phenyl}-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (1.38 g, 97%). LC/MS (ESI⁺) 486.4 (M+H)⁺.

Part B. The product from part A (0.80 g, 1.65 mmol) was stirred in anhydrous CH₂Cl₂ (10 mL) at RT under N₂. NaOAc (0.5 g, 6.10 mmol) and molecular sieves (4Å, 1.2 g) were added followed by the addition of PCC (0.89 g, 4.12 mmol). The resulting slurry was stirred at RT for 4 h. Analytical LC-MS showed completion of the reaction. The mixture was filtered, and rinsed with CH₂Cl₂. The filtrate was washed with H₂O (2x) and brine (2x), dried over Na₂SO₄, filtered, and concentrated to dryness to afford 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl}cyclopentanecarbaldehyde (0.78 g, yield: 99%). LC/MS (ESI⁺) 484.6 (M+H)⁺.

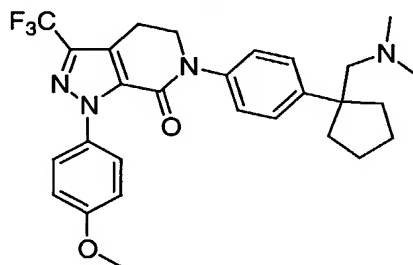
Part C. The product from part B (100 mg, 0.21 mmol) and methylamine hydrochloride (100 mg, excess) were stirred in dichloroethane (1.0 mL) in a capped vial. NaBH(OAc)₃ (200 mg, 0.94 mmol) was added followed by addition of three drops of HOAc. The reaction mixture was stirred at RT for 2h. Analytical LC-MS showed completion of the reaction. The mixture was evaporated and dissolved in aqueous MeOH.

It was then purified by prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run) to obtain 1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopentyl}phenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (35 mg, yield: 34%). LC/MS (ESI⁺) 499.4 (M+H)⁺, t_R = 4.85 min. ¹H NMR (acetone-d₆) δ 7.50 (m, 4H), 7.35 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 9.1 Hz, 2H), 4.17 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.39 (s, 2H), 3.16 (t, J = 6.3 Hz, 2H), 2.64 (s, 3H), 2.14-1.66 (m, 8H) ppm.

10

Example 28

6-(4-{1-[(dimethylamino)methyl]cyclopentyl}phenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



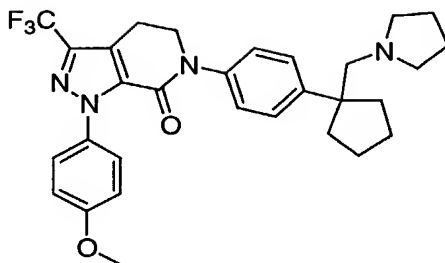
15

Following a procedure analogous to that used for Example 27, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 513.6 (M+H)⁺, t_R = 4.96 min. ¹H NMR (acetone-d₆) δ 7.52 (m, 4H), 7.38 (d, J = 8.5 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 4.19 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.60 (s, 2H), 3.17 (t, J = 6.3 Hz, 2H), 2.62 (s, 6H), 2.16-1.64 (m, 8H) ppm.

25

Example 29

1-(4-methoxyphenyl)-6-(4-{1-(1-pyrrolidinylmethyl)cyclopentyl}phenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt

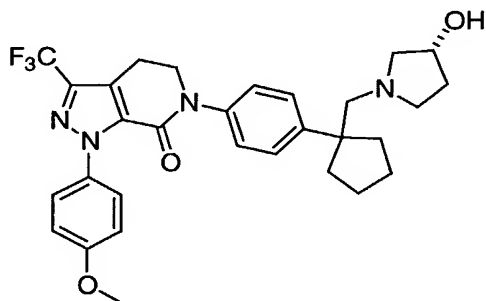


Following a procedure analogous to that used for Example 27, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run).

- 5 LC/MS (ESI⁺) 539.6 (M+H)⁺, *t_R* = 5.13 min. ¹H NMR (acetone-*d*₆) δ 7.52 (m, 4H), 7.40 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 4.19 (t, *J* = 6.3 Hz, 2H), 3.83 (s, 3H), 3.75 (s, 2H), 3.52 (m, 2H), 3.17 (t, *J* = 6.3 Hz, 2H), 2.92 (m, 2H), 2.18 (m, 2H), 2.04-1.62 (m, 10H) ppm. ¹⁹F NMR
- 10 (acetone-*d*₆) δ -62.17 (TFA salt), -79.82 (CF₃) ppm.

Example 30

- 6-[4-(1-[(3*R*)-3-hydroxy-1-pyrrolidinyl]methyl)cyclopentyl]phenyl]-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt
- 15

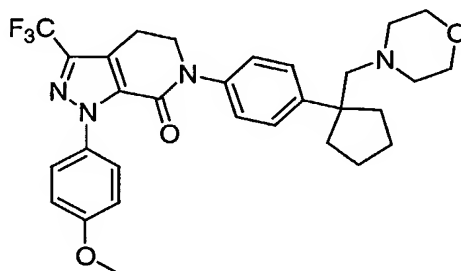


- Following a procedure analogous to that used for Example 27, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run).
- 20 LC/MS (ESI⁺) 555.6 (M+H)⁺, *t_R* = 4.77 min. ¹H NMR (acetone-*d*₆) δ 7.52 (m, 4H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 4.36 (s, br, 1H), 4.19 (t, *J* = 6.3 Hz, 2H), 3.83 (s, 3H), 3.72 (m, 2H), 3.59 (m, 2H), 3.17 (t, *J* = 6.3

Hz, 2H), 2.92 (m, 2H), 2.16-1.63 (m, 10H) ppm. ^{19}F NMR (acetone- d_6) δ -62.16 (TFA salt), -76.70 (CF_3) ppm.

Example 31

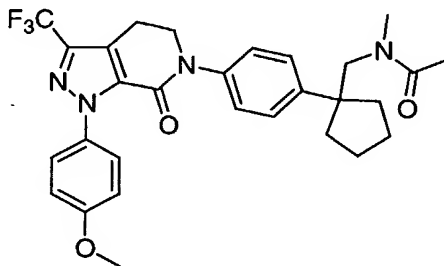
5 **1-(4-methoxyphenyl)-6-{4-[1-(4-morpholinylmethyl)cyclopentyl]phenyl}-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt**



10 Following a procedure analogous to that used for Example 27, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ in a 10-min run). LC/MS (ESI $^+$) 555.6 ($\text{M}+\text{H}$) $^+$, t_R = 4.49 min. ^1H NMR (acetone- d_6) δ 7.43 (m, 4H), 7.28 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 4.09 (t, J = 6.6 Hz, 2H), 3.74 (s, 3H), 3.65 (m, 4H), 3.50 (s, 2H), 3.33 (m, 2H), 3.07 (t, J = 6.3 Hz, 2H), 2.89 (m, 2H), 2.02-1.52 (m, 8H) ppm.

Example 32

20 ***N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl}cyclopentyl)methyl]-*N*-methylacetamide**

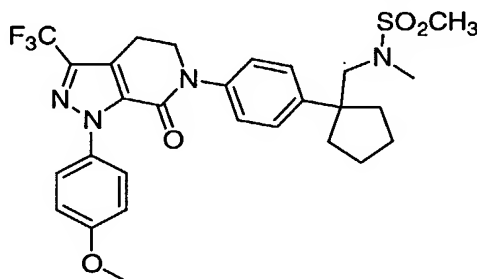


Following a procedure analogous to that used for Example 21, the title compound was prepared. The product was

purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run).
 LC/MS (ESI⁺) 541.6 (M+H)⁺, t_R = 6.50 min. ¹H NMR (acetone-
 d₆) δ 7.49 (dd, J = 8.8, 1.8 Hz, 2H), 7.34 (m, 4H), 6.97
 (dd, J = 8.8, 1.8 Hz, 2H), 4.17 (t, J = 6 Hz, 2H), 3.82 (s,
 5 3H), 3.52 (s, 2H), 3.17 (t, J = 6 Hz, 2H), 2.34 (s, 3H),
 2.03-1.59 (m, 11H) ppm.

Example 33

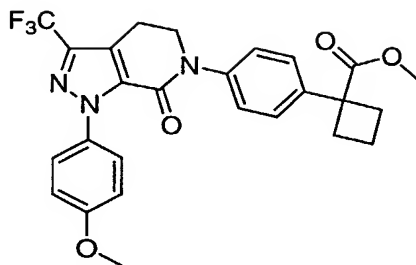
**N-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-
 10 1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-
 yl]phenyl}cyclopentyl)methyl]-N-methylmethanesulfonamide**



Following a procedure analogous to that used for Example
 23, the title compound was prepared. The product was
 15 purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run).
 LC/MS (ESI⁺) 577.4 (M+H)⁺, t_R = 6.74 min. ¹H NMR (acetone-
 d₆) δ 7.50 (d, J = 9 Hz, 2H), 7.35 (m, 4H), 6.98 (d, J = 9
 Hz, 2H), 4.18 (t, J = 6.5 Hz, 2H), 3.83 (s, 3H), 3.22 (s,
 2H), 3.17 (t, J = 6.5 Hz, 2H), 2.70 (s, 3H), 2.17 (s, 3H),
 20 2.13 (m, 2H), 1.80 (m, 4H), 1.64 (m, 2H) ppm.

Example 34

**methyl 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-
 1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-
 25 yl]phenyl}cyclobutanecarboxylate**



Part A. 1-Phenyl-1-cyclobutylcarbonitrile (5.0 g, 31.83 mmol) and KOH (85%, 6.29 g, 95.49 mmol, 3 eq) were heated in ethylene glycol (10 mL) at 185-190°C for 6h under N₂.

5 LC-MS showed completion of the reaction. H₂O was added to the cooled mixture. It was extracted with Et₂O (3x). The aqueous layer was acidified with conc. HCl, and then extracted with CHCl₃ (2x). The chloroform layer was washed with H₂O, brine, dried over MgSO₄, filtered, and
10 concentrated to dryness to give 1-phenyl-1-cyclobutyl carboxylic acid (4.43 g, yield: 79.2%). LC/MS (ESI⁺) 177.4 (M+H)⁺, t_R = 2.56 min (10-90% CH₃CN/H₂O in a 6-min run).

Part B. The product from part A (4.43 g, 25.2 mmol) was
15 stirred in HOAc (20 mL) at RT under N₂. I₂ (6.40 g, 25.2 mmol) was added, followed by the addition of NaIO₃ (1.25 g, 6.3 mmol) and conc. H₂SO₄ (0.5 mL). The resulting mixture was stirred at 70°C for 2 days. LC-MS showed completion of the reaction. The cooled mixture was poured into H₂O, and
20 extracted with EtOAc. The organic layer was washed with sodium thiosulfate, brine, dried over MgSO₄, filtered, and concentrated to dryness to give 4-iodophenylcyclobutyl carboxylic acid (6.49 g, 85%). LC/MS (ESI⁺) 303.2 (M+H)⁺, t_R = 2.55 min (10-90% CH₃CN/H₂O in a 4-min run).

25

Part C. The product from part B (1.20 g, 3.97 mmol) and 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (0.87 g, 2.8 mmol) were stirred in DMSO (3 mL) under N₂. K₂CO₃ (1.16 g, mmol, 3.0

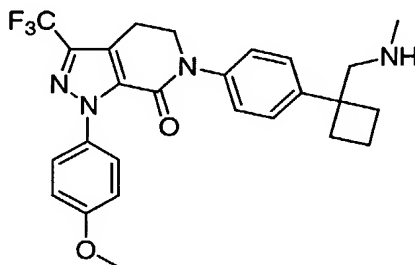
eq) was added followed by the addition of 1,10-phenanthroline (100 mg, 20 mol%) and CuI (106 mg, 20 mol%). The resulting mixture was stirred at 130°C overnight. LC-MS showed completion of the reaction. EtOAc was added to the cooled solution. The solution was acidified with 1N HCl, and the organic layer was washed with H₂O and brine, dried over MgSO₄, filtered, and concentrated to afford 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl}cyclobutane carboxylic acid (1.34 g, yield 97%). LC/MS (ESI⁺) 486.6 (M+H)⁺, t_R = 2.81 min (10-90% CH₃CN/H₂O in a 4-min run).

Part D. The product from part C (50 mg, 0.103 mmol) was dissolved in MeOH (5 mL), and conc. HCl (0.5 mL) was added. The resulting mixture was stirred at reflux for 2 h. After cooling, the mixture was purified by prep LC-MS (35-98% CH₃CN in H₂O) to afford the title compound (35 mg, yield: 68%). LC/MS (ESI⁺) 499.4 (M+H)⁺, t_R = 5.70 min. ¹H NMR (CDCl₃) δ 7.45 (d, J = 8.8 Hz, 2H), 7.28 (AA'BB', J = 8 Hz, 4H), 6.91 (d, J = 8.8 Hz, 2H), 4.13 (t, J = 6.9 Hz, 2H), 3.80 (s, 3H), 3.63 (s, 3H), 3.15 (t, J = 6.6 Hz, 2H), 2.81 (m, 2H), 2.48 (m, 2H), 2.03 (m, 1H), 1.86 (m, 1H) ppm.

25

Example 35

1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclobutyl}phenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



30

Part A. The product from part C of Example 34 (1.32 g, 2.72 mmol) was stirred in THF (10 mL) at 0°C under N₂. Et₃N (0.59 mL, 4.08 mmol, 1.5 eq) was added followed by dropwise addition of ClCO₂Et (0.38 mL, 3.54 mmol, 1.3 eq). The
5 reaction mixture was then stirred at 0°C for 30 min. TLC showed completion of the reaction. The mixture was filtered and rinsed with anhydrous THF. The THF filtrate (ca. 20 mL) was stirred at 0°C under N₂. MeOH (4 mL) was added followed by the addition of NaBH₄ (1.03 g, 27.10
10 mmol, 10 eq). The resulting mixture was stirred at 0°C for 40 min. Analytical LC-MS showed completion of the reaction. Sat'd Na₂SO₄ was then added. The mixture was extracted with EtOAc (2x). The organic layer was washed with H₂O(2x) and brine (2x), dried over Na₂SO₄, filtered,
15 and concentrated to dryness to give 6-{4-[1-(hydroxymethyl)cyclobutyl]phenyl}-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (1.30 g, 99%). LC/MS (ESI⁺) 472.6 (M+H)⁺, t_R = 2.84 min (10-90% CH₃CN/H₂O in a 4-min run).

20

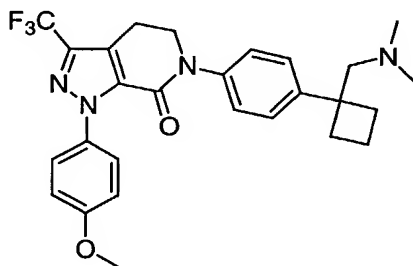
Part B. The product from part A (0.90 g, 1.91 mmol) was stirred in anhydrous CH₂Cl₂ (10 mL) at RT under N₂. NaOAc (0.32 g, 3.82 mmol, 2.0 eq) and molecular sieves (4A, 0.90 g) were added followed by the addition of PCC (0.69 g, 2.87
25 mmol, 1.5 eq). The resulting slurry was stirred at RT for 4 h. Analytical LC-MS showed completion of the reaction. The mixture was filtered and rinsed with CH₂Cl₂. The filtrate was washed with H₂O (2x) and brine (2x), dried over Na₂SO₄, filtered, and concentrated to dryness to afford
30 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl}cyclobutanecarbaldehyde (0.88 g, yield: 99%). LC/MS (ESI⁺) 470.6 (M+H)⁺, t_R = 3.01 min (10-90% CH₃CN/H₂O in a 4-min run).

Part C. The product from part B (500 mg, 1.04 mmol), methylamine hydrochloride (200 mg, excess) were stirred in dichloroethane (15 mL) at RT under N₂. NaBH(OAc)₃ (1.03 g, 4.86 mmol) was added followed by addition of three drops of HOAc. The reaction mixture was stirred at RT for 2.5 h. Analytical LC-MS showed completion of the reaction. The mixture was evaporated, and dissolved in aqueous MeOH. It was then purified by prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run) to obtain 1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclobutyl}phenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (230 mg, 46%). LC/MS (ESI⁺) 485.4 (M+H)⁺, t_R = 4.93 min. ¹H NMR (acetone-d₆) δ 7.51 (d, 2H), 7.33 (m, 4H), 6.99 (d, 2H), 4.17 (m, 2H), 3.83 (s, 3H), 3.62 (m, 2H), 3.17 (m, 2H), 2.73 (s, 3H), 2.46 (m, 4H), 2.15-1.86 (m, 2H) ppm. ¹⁹F NMR (acetone-d₆) δ -62.18 (TFA), -76.65 (CF₃) ppm.

20

Example 36

6-(4-{1-[(dimethylamino)methyl]cyclobutyl}phenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



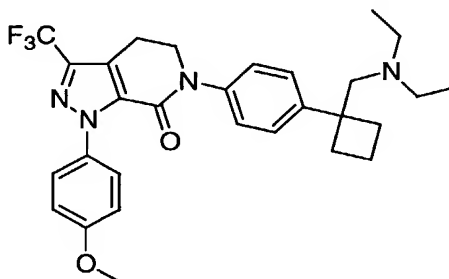
25 Following a procedure analogous to that used for Example 35, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 499.6 (M+H)⁺, t_R = 4.75 min. ¹H NMR (acetone-d₆) δ 7.49 (m, 4H), 7.39 (d, J = 8.0 Hz, 2H), 6.98 (d, J =

9.1 Hz, 2H), 4.19 (t, J = 6.4 Hz, 2H), 3.83 (s, 3H), 3.77 (m, 2H), 3.17 (t, J = 6.3 Hz, 2H), 2.68 (s, 6H), 2.48 (t, J = 7.5 Hz, 4H), 2.09 (m, 1H), 1.89 (m, 1H) ppm.

5

Example 37

6-(4-{1-[(diethylamino)methyl]cyclobutyl}phenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



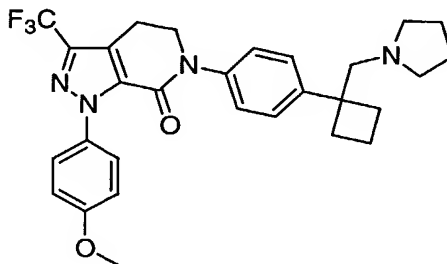
10 Following a procedure analogous to that used for Example 35, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 527.6 (M+H)⁺, t_R = 5.04 min. ¹H NMR (acetone-*d*₆) δ 7.53 (m, 4H), 7.39 (d, J = 8.5 Hz, 4H), 6.98 (d, J = 9.1 Hz, 2H), 4.19 (t, J = 6.3 Hz, 2H), 3.83 (s, 3H), 3.68 (s, 2H), 3.17 (t, J = 6.3 Hz, 2H), 2.95 (m, 4H), 2.48 (t, J = 7.8 Hz, 4H), 2.10-1.85 (m, 2H), 1.16 (m, 6H) ppm.

15

Example 38

20

1-(4-methoxyphenyl)-6-{4-[1-(1-pyrrolidinylmethyl)cyclobutyl]phenyl}-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



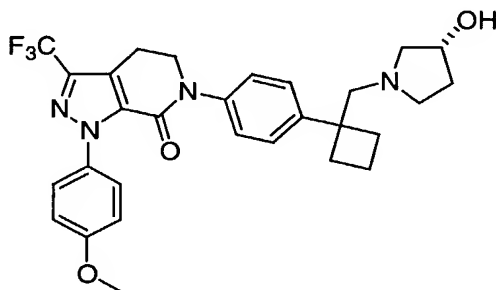
Following a procedure analogous to that used for Example 35, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 525.6 (M+H)⁺, t_R = 4.97 min. ¹H NMR (acetone-*d*₆) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.39 (m, 4H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.87 (m, 2H), 3.83 (s, 3H), 3.51 (m, 2H), 3.17 (t, *J* = 6.3 Hz, 2H), 2.93 (m, 2H), 2.47 (m, 4H), 2.09-1.85 (m, 6H) ppm. ¹⁹F NMR (acetone-*d*₆) δ -62.16 (TFA), -76.74 (CF₃) ppm.

10

Example 39

6-[4-(1-[[(3*R*)-3-hydroxy-1-pyrrolidinyl]methyl]cyclobutyl)phenyl]-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt

15



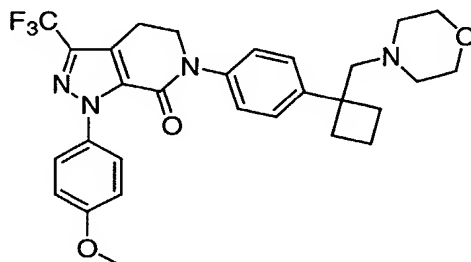
Following a procedure analogous to that used for Example 35, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run).

LC/MS (ESI⁺) 541.6 (M+H)⁺, t_R = 4.77 min. ¹H NMR (acetone-*d*₆) δ 7.51 (d, *J* = 8.9 Hz, 2H), 7.39 (m, 4H), 6.98 (d, *J* = 9.1 Hz, 2H), 4.33 (m, 1H), 4.20 (t, *J* = 6.5 Hz, 2H), 3.83 (m, 7H), 3.52 (m, 2H), 3.17 (t, *J* = 6.5 Hz, 2H), 2.47 (m, 4H), 2.14-1.84 (m, 4H). ¹⁹F NMR (acetone-*d*₆) δ -62.16 (TFA), -76.34 (CF₃) ppm.

25

Example 40

1-(4-methoxyphenyl)-6-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt

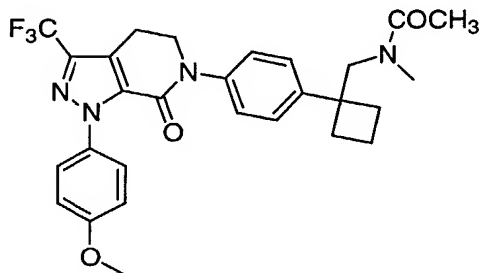


Following a procedure analogous to that used for Example 35, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run).

LC/MS (ESI⁺) 541.6 (M+H)⁺, t_R = 4.86 min. ¹H NMR (acetone-*d*₆) δ 7.49 (m, 4H), 7.37 (m, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.18 (m, 2H), 3.83 (s, 3H), 3.74 (m, 8H), 3.17 (t, *J* = 6.5 Hz, 2H), 3.00 (m, 2H), 2.46 (m, 4H), 1.86 (m, 2H) ppm.

Example 41

***N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl}cyclobutyl)methyl]-*N*-methylacetamide**

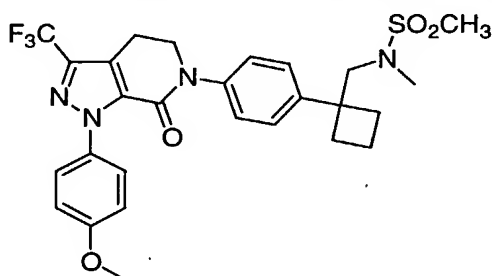


Following a procedure analogous to that used for Example 21, the title compound was prepared by using the product from Example 37 and acetyl chloride as the starting material. The mixture was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 527.2 (M+H)⁺, t_R = 6.36 min. ¹H NMR (acetone-*d*₆) δ 7.50 (d, *J* = 9.2 Hz, 2H),

7.33 (d, $J = 8.7$ Hz, 2H), 7.24 (m, 2H), 6.98 (d, $J = 9.2$ Hz, 2H), 4.17 (d, $J = 6.6$ Hz, 2H), 3.83 (s, 3H), 3.71, 3.67 (s, 2H), 3.17 (t, $J = 6.5$ Hz, 2H), 2.76, 2.45 (s, 3H), 2.35 (m, 2H), 2.18 (m, 1H), 2.08 (m, 1H), 1.76 (m, 2H), 1.33 (m, 1H) ppm.

Example 42

***N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclobutyl)methyl]-*N*-methylethanesulfonamide**

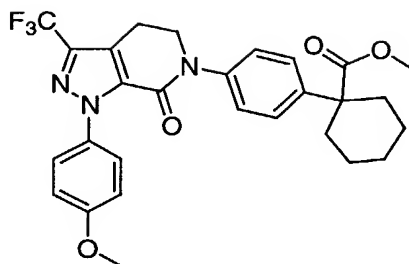


Following a procedure analogous to that used for Example 23, the title compound was prepared. The mixture was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run).

LC/MS (ESI⁺) 563.2 (M+H)⁺, $t_R = 6.62$ min. ¹H NMR (acetone-*d*₆) δ 7.50 (d, $J = 8.8$ Hz, 4H), 7.34 (d, $J = 8.5$ Hz, 2H), 7.23 (d, $J = 8.4$ Hz, 2H), 6.98 (d, $J = 8.8$ Hz, 2H), 4.18 (d, $J = 6.6$ Hz, 2H), 3.83 (s, 3H), 3.45 (s, 2H), 3.17 (t, $J = 6.5$ Hz, 2H), 2.70 (s, 3H), 2.38 (m, 2H), 2.28 (s, 3H), 2.26 (m, 2H), 2.03 (m, 1H), 1.81 (m, 1H) ppm.

Example 43

1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]-phenyl}cyclohexanecarboxylic acid methyl ester



Part A. 1-Phenyl-cyclohexylcarboxylic acid (3.0 g, 14.70 mmol) was stirred in HOAc (10 mL) at RT under N₂. I₂ (3.73 g, 14.70 mmol) was added, followed by the addition of NaIO₃ (0.72 g, 3.64 mmol) and conc. H₂SO₄ (0.2 mL). The resulting mixture was stirred at 70°C for 2 days. LC-MS showed the majority was the desired product. After partial evaporation, the cooled mixture was poured into H₂O and extracted with EtOAc. The organic layer was washed with sodium thiosulfate and brine, dried over MgSO₄, filtered, and concentrated to dryness to give almost pure 4-iodophenylcyclohexylcaroxylic acid (4.56 g, yield: 93.7%). LC/MS (ESI⁺) 331.4 (M+H)⁺, t_R = 3.96 min (10-90% CH₃CN/H₂O in a 6-min run).

15

Part B. The product of part A (0.70 g, 2.25 mmol) and 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (0.70 g, 2.25 mmol) were stirred in DMSO (3 mL) under N₂. K₂CO₃ (0.93 g, mmol, 3.0 eq) was added, followed by the addition of 1,10-phenanthroline (80 mg, 20 mmol%) and CuI (85 mg, 20mmol%). The resulting mixture was stirred at 130°C for 2 days. LC-MS showed completion of the reaction. EtOAc was added to the cooled solution. It was acidified with 1N HCl; and the organic layer was washed with H₂O and brine, dried over MgSO₄, filtered, and concentrated. LC/MS (ESI⁺) 514.4 (M+H)⁺. The residue (50 mg) was dissolved in MeOH (5 mL), and conc. HCl (0.5 mL) was added. The resulting mixture was stirred at 60°C for 4 h. After cooling, the mixture was purified by prep LC-MS (35-98% CH₃CN in H₂O) to give

30

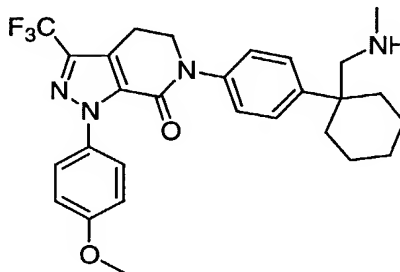
pure 1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]-phenyl}cyclohexanecarboxylic acid methyl ester (43 mg, yield: 83.7%). LC/MS (ESI⁺) 528.4 (M+H)⁺, t_R = 6.38 min.

5 ¹H NMR (CDCl₃) δ 7.45 (d, J = 9.1 Hz, 2H), 7.32 (AA'BB', J = 8.6 Hz, 4H), 6.92 (d, J = 8.8 Hz, 2H), 4.13 (t, J = 6.6 Hz, 2H), 3.81 (s, 3H), 3.63 (s, 3H), 3.15 (t, J = 6.6 Hz, 2H), 2.45 (m, 2H), 1.72-1.24 (m, 8H) ppm.

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Example 44

1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclohexyl}phenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



15

Part A. The product from part B of Example 43 (1.34 g, 2.61 mmol) was stirred in THF (10 mL) at 0°C under N₂. Et₃N (0.55 mL, 3.92 mmol, 1.5 eq) was added followed by dropwise addition of ClCO₂Et (0.33 mL, 3.34 mmol, 1.3 eq). The reaction mixture was then stirred at 0°C for 20 min. TLC showed completion of the reaction. The mixture was filtered, and rinsed with anhydrous THF. The THF filtrate (ca. 20 mL) was stirred at 0°C under N₂. MeOH (3.5 mL) was added followed by the addition of NaBH₄ (1.00 g, 26.3 mmol, 10 eq). The resulting mixture was stirred at 0°C for 40 min. Analytical LC-MS showed completion of the reaction. Sat'd Na₂SO₄ was then added. The mixture was extracted with EtOAc (2x). The organic layer was washed with H₂O (2x) and brine (2x), dried over Na₂SO₄, filtered, and concentrated to

dryness to give 6-{4-[1-(hydroxymethyl)cyclohexyl]phenyl}-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (1.21 g, yield 92.8%).

LC/MS (ESI⁺) 500.6 (M+H)⁺, t_R = 3.06 min (10-90% CH₃CN/H₂O

5 in a 4-min run). ¹H NMR (CDCl₃) δ 7.46 (d, J = 8.8 Hz, 2H), 7.34 (AA'BB', J = 8.4 Hz, 4H), 6.92 (d, J = 8.8 Hz, 2H), 4.15 (t, J = 6.7 Hz, 2H), 3.81 (s, 3H), 3.49 (s, 2H), 3.16 (t, J = 6.6 Hz, 2H), 2.24 (m, 2H), 2.13 (m, 2H), 1.56 (m, 4H), 1.34 (m, 2H) ppm.

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Part B. The product from part A (0.56 g, 1.12 mmol) was stirred in anhydrous CH₂Cl₂ (10 mL) at RT under N₂. NaOAc (0.37 g, 4.48 mmol, 4 eq) and molecular sieves (4Å, 1.0 g) were added followed by the addition of PCC (0.73 g, 3.36
15 mmol, 3 eq). The resulting slurry was stirred at RT for 1.5h. Analytical LC-MS showed completion of the reaction. The mixture was filtered, and rinsed with CH₂Cl₂. The filtrate was washed with H₂O (2x) and brine (2x), dried over Na₂SO₄, filtered, and concentrated to dryness to afford
20 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl}cyclohexanecarbaldehyde (0.54 g, yield: 100%).
LC/MS (ESI⁺) 498.6 (M+H)⁺, t_R = 3.20 min (10-90% CH₃CN in H₂O in a 4-min run).

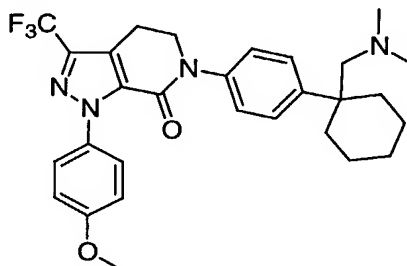
25

Part C. The product from part B (0.4 g, 0.85 mmol) and methylamine hydrochloride (0.2 mg, 2.99 mmol, excess) were stirred in dichloroethane (8 mL) at RT under N₂. NaBH(OAc)₃ (0.85 mg, 4.01 mmol) was added followed by addition of HOAc
30 (0.1 mL). The reaction mixture was stirred at RT for 2h. Analytical LC-MS showed completion of the reaction. The mixture was evaporated, and dissolved in aqueous MeOH. The mixture was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run) to afford 1-(4-methoxyphenyl)-6-(4-{1-

[(methylamino)methyl]cyclohexyl}phenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (120 mg. Yield: 29%). LC/MS (ESI⁺) 513.4 (M+H)⁺, t_R = 4.97 min. ¹H NMR (acetone-*d*₆) δ 7.52 (m, 4H), 7.38 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 4.19 (t, J = 6.3 Hz, 2H), 3.81 (s, 3H), 3.60 (s, 2H), 3.17 (t, J = 6.3 Hz, 2H), 2.62 (s, 6H), 2.16-1.64 (m, 8H) ppm.

Example 45

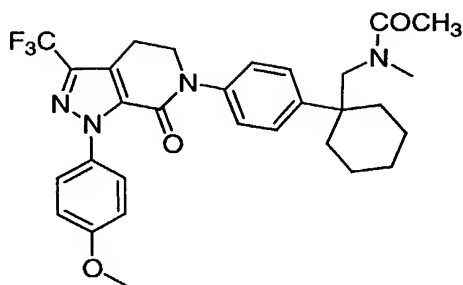
6-(4-{1-[(dimethylamino)methyl]cyclohexyl}phenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for Example 44, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 526.4 (M+H)⁺. ¹H NMR (acetone-*d*₆) δ 7.52 (m, 4H), 7.38 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 4.19 (t, J = 6.3 Hz, 2H), 3.81 (s, 3H), 3.60 (s, 2H), 3.17 (t, J = 6.3 Hz, 2H), 2.62 (s, 6H), 2.16-1.64 (m, 8H) ppm.

Example 46

N-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl}cyclohexyl)methyl]-*N*-methylacetamide



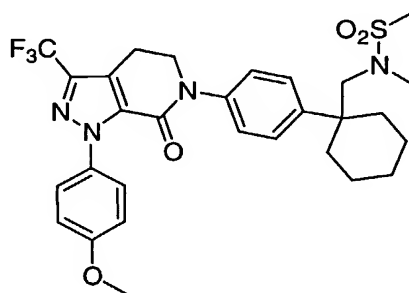
Following a procedure analogous to that used for Example 21, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run).

5 LC/MS (ESI⁺) 555.2 (M+H)⁺, *t*_R = 6.76 min. ¹H NMR (acetone-*d*₆) δ 7.50 (d, *J* = 8.8 Hz, 2H), 7.38 (m, 4H), 6.98 (d, *J* = 9.2 Hz, 2H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.83 (s, 3H), 3.39 (m, 2H), 3.17 (t, *J* = 6.4 Hz, 2H), 2.70, 2.42 (s, 3H), 2.02, 1.93 (m, 3H), 1.56 (m, 6H), 1.40 (m, 4H) ppm.

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Example 47

***N*-[(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclohexyl)methyl]-*N*-methylethanesulfonamide**



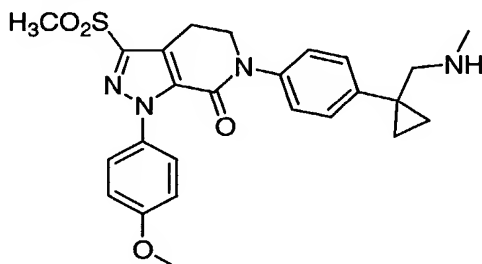
15

Following a procedure analogous to that used for Example 23, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run).

20 LC/MS (ESI⁺) 591.2 (M+H)⁺, *t*_R = 6.90 min. ¹H NMR (acetone-*d*₆) δ 7.50 (d, *J* = 8.8 Hz, 2H), 7.42 (AA'BB', *J* = 8.8 Hz, 4H), 6.98 (d, *J* = 8.7 Hz, 2H), 4.19 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 3.17 (t, *J* = 6.6 Hz, 2H), 3.10 (s, 2H), 2.69 (m, 3H), 2.21 (m, 3H), 1.57 (m, 6H), 1.29 (m, 4H) ppm.

Example 48

**1-(4-methoxyphenyl)-6-(4-{1-
[(methylamino)methyl]cyclopropyl}phenyl)-3-
(methylsulfonyl)-1,4,5,6-tetrahydro 7H-pyrazolo[3,4-
c]pyridin-7-one, trifluoroacetic acid salt**



Part A. 3-Chloro-5,6-dihydro-2(1H)-pyridinone (10.0 g, 38.17 mmol) and (1Z)-1-[chloro(methylsulfonyl)methylene]-2-(4-methoxyphenyl)hydrazine (5.0 g, 38.17 mmol) were stirred in toluene (200 mL) at RT under N₂. Et₃N (30 mL, 215.24 mmol) in toluene (150 mL) was added dropwise to the solution. After addition, the mixture was heated at 85°C overnight. After cooling, H₂O was added. It was extracted with EtOAc (2x). The organic layers were washed with H₂O (2x) and brine, dried over MgSO₄, filtered, and concentrated to dryness. The residue was purified by flash column chromatography (silica gel, CH₂Cl₂, then CH₂Cl₂: EtOAc = 1:1, then EtOAc) to give 1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (3.85 g, yield: 31%). LC/MS (ESI⁺) 322.4 (M+H)⁺, t_R = 1.79 min (10-90% CH₃CN/H₂O in a 4-min run).

Part B. The product from part A (2.07 g, 6.23 mmol) and 4-iodophenylcyclopropylcarboxylic acid (2.75 g, 9.54 mmol, 1.5 eq) were stirred in DMSO (6 mL) under N₂. K₂CO₃ (2.57 g, 18.62 mmol, 3.0 eq) was added, followed by the addition of CuI (0.24 g, 20mol%) and 1,10-phenanthroline (0.23 g, 20 mol%). The resulting mixture was heated at 130°C overnight. After cooling, 1N HCl was added to acidify the solution. It was extracted with EtOAc (2x), washed with H₂O and

brine, dried over MgSO_4 , filtered, and concentrated to dryness to give 1-{4-[1-(4-methoxyphenyl)-3-(methanesulfonyl)-7-oxo-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl}cyclopropanecarboxylic acid (2.95 g, 5 yield: 95%). LC/MS (ESI^+) 482.4 ($\text{M}+\text{H}^+$), $t_R = 2.25$ min (10-90% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ in a 4-min run).

Part C. The product from part B (2.21 g, 4.59 mmol) was stirred in THF (15 mL) at 0°C under N_2 . Et_3N (0.96 mL, 6.89 10 mmol, 1.5 eq) was added, followed by dropwise addition of ClCO_2Et (0.57 mL, 5.48 mmol, 1.2 eq). The reaction mixture was then stirred at 0°C for 40 min. TLC showed completion of the reaction. The mixture was filtered, and rinsed with anhydrous THF. The THF filtrate (ca. 20 mL) was stirred at 15 0°C under N_2 . MeOH (4 mL) was added, followed by portionwise addition of NaBH_4 (1.62 g, 42.63 mmol, 9 eq). The resulting mixture was stirred at 0°C for 35 min. Analytical LC-MS showed completion of the reaction. Sat'd Na_2SO_4 was then added. The mixture was extracted with EtOAc 20 (2x). The organic layer was washed with H_2O (2x) and brine (2x), dried over Na_2SO_4 , filtered, and concentrated to dryness to give 6-{4-[1-(hydroxymethyl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-(methanesulfonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (0.23 g, 84.7%). LC/MS 25 (ESI^+) 468.4 ($\text{M}+\text{H}^+$), $t_R = 2.24$ min (10-90% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ in a 4-min run).

Part D. The product from part C (1.52 g, 3.27 mmol) was stirred in anhydrous CH_2Cl_2 (15 mL) at RT under N_2 . NaOAc 30 (0.54 g, 6.54 mmol, 2.0 eq) and molecular sieves (4\AA , 1.5 g) were added, followed by the addition of PCC (1.06 g, 4.90 mmol, 1.5 eq). The resulting slurry was stirred at RT for 2 h. Analytical LC-MS showed completion of the reaction. The mixture was filtered through Celite®, and

rinsed with CH₂Cl₂. The filtrate was washed with H₂O (2x) and brine (2x), dried over Na₂SO₄, filtered, and concentrated to dryness to give 1-{4-[1-(4-methoxyphenyl)-3-(methylsulfonyl)-7-oxo-1,4,5,7-tetrahydro-6H-

5 pyrazolo[3,4-c]pyridin-6-yl]phenyl}cyclopropanecarbaldehyde (1.35 g, yield: 89%). LC/MS (ESI⁺) 466.4 (M+H)⁺, *t_R* = 2.38 min (10-90% CH₃CN/H₂O in a 4-min run).

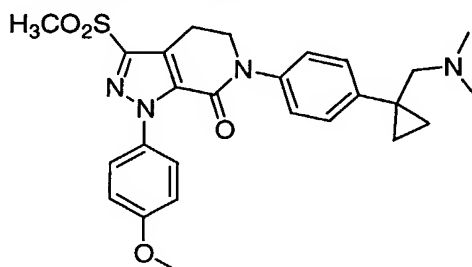
Part E. The product from Part E (100 mg, 0.22 mmol) and 10 methylamine hydrochloride (50 mg, excess) were stirred in dichloroethane (1 mL) in a capped vial. NaBH(OAc)₃ (250 mg, 1.16 mmol) was added followed by addition of one drop of HOAc. The reaction mixture was stirred at RT for 1.5 h. Analytical LC-MS showed completion of the reaction. The 15 mixture was evaporated, and dissolved in aqueous MeOH. It was then purified by prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run) to obtain the product 1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro 7H-pyrazolo[3,4-

20 c]pyridin-7-one (33 mg, 31.3%). LC/MS (ESI⁺) 481.4 (M+H)⁺, *t_R* = 3.99 min. ¹H NMR (acetone-*d*₆) δ 7.53 (m, 4H), 7.32 (d, *J* = 7.7 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 4.13 (t, *J* = 6.4 Hz, 2H), 3.83 (s, 3H), 3.46 (m, 2H), 3.26 (m, 5H), 2.80 (m, 3H), 1.11 (m, 2H), 1.00 (m, 2H) ppm.

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Example 49

6-(4-{1-[(dimethylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



30

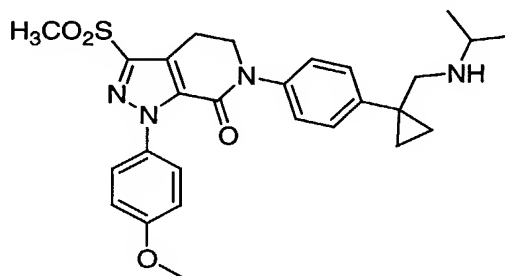
Following a procedure analogous to that used for the preparation of Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 495.6 (M+H)⁺, t_R = 4.06 min.

5 ¹H NMR (acetone-d₆) δ 7.55 (m, 4H), 7.38 (d, J = 7.5 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 4.16 (d, J = 6.6 Hz, 2H), 3.86 (m, 3H), 3.71 (m, 2H), 3.64 (m, 2H), 3.29, 3.25 (m, 6H), 3.09 (t, J = 6.6 Hz, 2H), 2.99 (m, 3H), 1.17 (m, 2H), 1.13 (m, 2H) ppm.

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Example 50

6-(4-{1-[(isopropylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



15

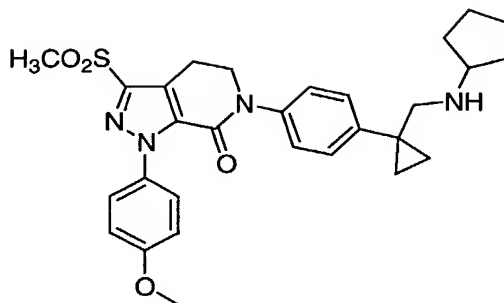
Following a procedure analogous to that used for the preparation of Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 509.6 (M+H)⁺, t_R = 4.34 min.

20 ¹H NMR (acetone-d₆) δ 7.58 (m, 4H), 7.33 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 9.1 Hz, 2H), 4.52 (m, 1H), 4.16 (d, J = 6.6 Hz, 2H), 3.86 (s, 3H), 3.79 (m, 2H), 3.61 (m, 1H), 3.48 (m, 2H), 3.29 (m, 5H), 1.33 (d, J = 6.2 Hz, 2H), 1.17 (m, 2H), 1.07 (m, 2H) ppm.

25

Example 51

6-(4-{1-[(cyclopentylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt,



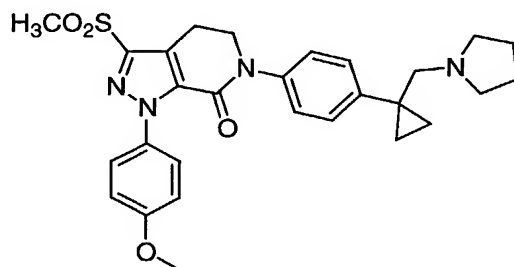
Following a procedure analogous to that used for the preparation of Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O

5 in a 10-min run). LC/MS (ESI⁺) 535.4 (M+H)⁺, *t_R* = 4.30 min.

¹H NMR (acetone-*d*₆) δ 7.55 (m, 4H), 7.33 (d, *J* = 7.4 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 4.16 (t, *J* = 6.6 Hz, 2H), 3.85 (s, 3H), 3.64 (m, 1H), 3.44 (m, 2H), 3.09 (m, 2H), 2.05 (m, 2H), 1.70 (m, 4H), 1.53 (m, 2H), 1.16 (m, 2H),
10 0.98 (m, 2H) ppm.

Example 52

**1-(4-methoxyphenyl)-3-(methylsulfonyl)-6-{4-[1-(1-pyrrolidinylmethyl)cyclopropyl]phenyl}-1,4,5,6-tetrahydro-
15 7H-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt**



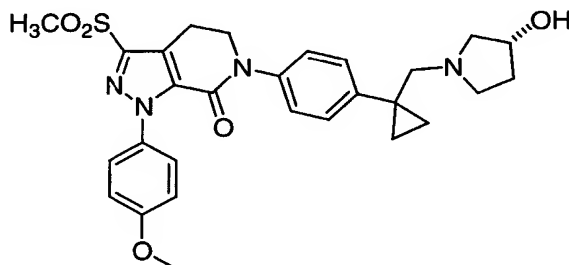
Following a procedure analogous to that used for the preparation of Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O

20 in a 10-min run). LC/MS (ESI⁺) 521.4 (M+H)⁺, *t_R* = 4.07 min.

¹H NMR (acetone-*d*₆) δ 7.58 (m, 4H), 7.37 (d, *J* = 7.7 Hz, 2H), 7.02 (d, *J* = 7.7 Hz, 2H), 4.19 (t, *J* = 6.6 Hz, 2H), 3.85 (s, 3H), 3.70 (m, 4H), 3.28 (m, 5H), 3.09 (t, *J* = 6.6 Hz, 2H), 2.08-2.03 (m, 2H), 1.16 (m, 2H), 1.06 (m, 2H) ppm.

Example 53

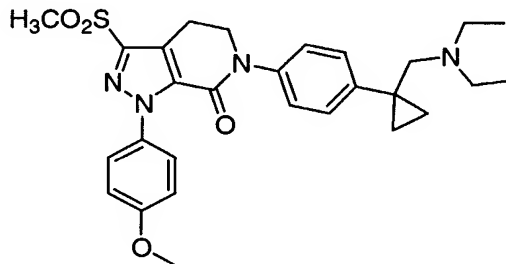
6-[4-(1-[(3R)-3-hydroxy-1-pyrrolidinyl]methyl)cyclopropyl]phenyl]-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for the preparation of Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 537.6 (M+H)⁺, *t_R* = 3.90 min. ¹H NMR (acetone-*d*₆) δ 7.55 (m, 4H), 7.38 (m, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 4.52 (m, 1H), 4.17 (m, 2H), 3.85 (s, 3H), 3.79 (m, 2H), 3.63 (m, 2H), 3.29 (m, 5H), 3.09 (m, 2H), 2.17 (m, 2H), 1.17 (m, 2H), 1.07 (m, 2H) ppm.

Example 54

6-(4-{1-[(diethylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



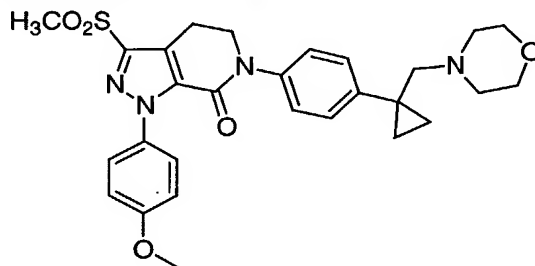
Following a procedure analogous to that used for the preparation of Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 523.4 (M+H)⁺, *t_R* = 4.54 min.

¹H NMR (acetone-*d*₆) δ 7.55 (m, 4H), 7.35 (d, *J* = 7.5 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 4.16 (d, *J* = 6.6 Hz, 2H), 3.84 (s, 3H), 3.56 (m, 4H), 3.28 (m, 3H), 3.10 (m, 2H), 1.17 (m, 5H), 1.17 (m, 2H), 1.05 (m, 2H) ppm.

5

Example 55

1-(4-methoxyphenyl)-3-(methylsulfonyl)-6-{4-[1-(4-morpholinylmethyl)cyclopropyl]phenyl}-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-*c*]pyridin-7-one



10

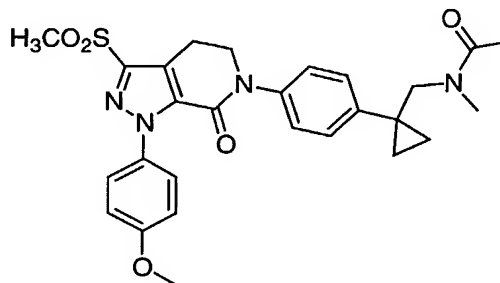
Following a procedure analogous to that used for the preparation of Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 537.6 (M+H)⁺, *t*_R = 4.18 min.

¹H NMR (acetone-*d*₆) δ 7.54 (m, 4H), 7.36 (d, *J* = 7.7 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 4.17 (t, *J* = 6.6 Hz, 2H), 3.83 (m, 7H), 3.68 (m, 2H), 3.61 (m, 2H), 3.25 (m, 5H), 3.15 (m, 2H), 2.08-2.03 (m, 2H), 1.18 (m, 2H), 1.07 (m, 2H) ppm.

20

Example 56

***N*-[(1-{4-[1-(4-methoxyphenyl)-3-(methylsulfonyl)-7-oxo-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)methyl]-*N*-methylacetamide**



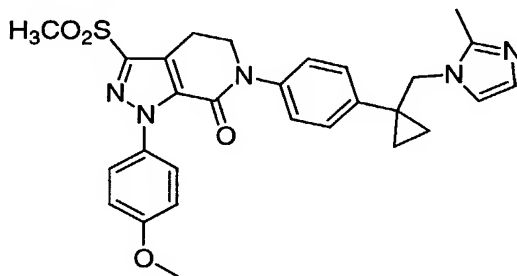
25

Following a procedure analogous to that used for the preparation of Example 21, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 523.6 (M+H)⁺, t_R = 5.07 min.

5

Example 57

3-methanesulfonyl-1-(4-methoxyphenyl)-6-{4-[1-(2-methylimidazol-1-ylmethyl)cyclopropyl]phenyl}-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one



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Part A. The product of part C in example 48 (0.69 g, 1.48 mmol) was stirred in CH₂Cl₂ (6 mL) at 0°C under N₂. PPh₃ (0.50 g, 1.91 mmol, 1.3 eq) was added, followed by the addition of CBr₄ (0.49 g, 1.48 mmol, 1.0 eq). The resulting mixture was stirred at 0°C for 30 min. LC-MS showed completion of the reaction (10-90% CH₃CN in H₂O in a 4-min run, t_R = 2.73 min). Sat'd NH₄Cl was then added. The mixture was extracted with EtOAc. The organic layer was washed with H₂O and brine, dried over MgSO₄, filtered, and concentrated to dryness (0.39 g, yield: 50%). The product was used directly in the next step. LC/MS (ESI⁺) 530.2, 532.2 (M+H)⁺.

Part B. The product of Part A (0.13 g, 0.25 mmol), 2-methylimidazole (50 mg, 0.64 mmol), and K₂CO₃ (0.13 g, 1.0 mmol) were stirred in DMF (0.4 mL) under N₂. The mixture was heated at 85-90°C for 30 min. LC-MS showed completion of the reaction. After cooling to RT, H₂O was added. The mixture was purified by prep LC-MS (15-70% CH₃CN in H₂O) to

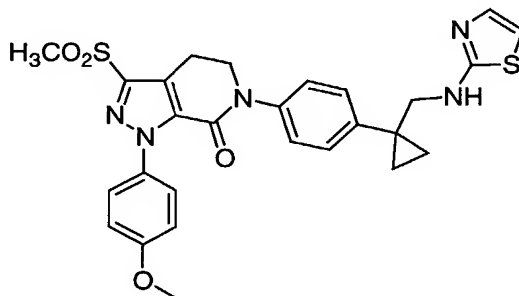
give pure 3-methanesulfonyl-1-(4-methoxyphenyl)-6-{4-[1-(2-methylimidazol-1-ylmethyl)cyclopropyl]phenyl}-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one (36 mg, yield %).

LC/MS (ESI⁺) 532.4 (M+H)⁺, t_R = 4.43 min. ¹H NMR (acetone-
 5 d_6) δ 7.57 (m, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.45 (m, 1H),
 7.26 (AA'BB', J = 8.4 Hz, 4H), 6.99 (d, J = 9.1 Hz, 2H),
 4.41 (s, 2H), 4.13 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.25
 (m, 5H), 2.11 (s, 3H), 1.27 (t, J = 5.8 Hz, 2H), 1.03 (t, J
 = 5.8 Hz, 2H) ppm.

10

Example 58

3-methanesulfonyl-1-(4-methoxyphenyl)-6-{4-[1-(thiazol-2-ylaminomethyl)cyclopropyl]phenyl}-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one



15

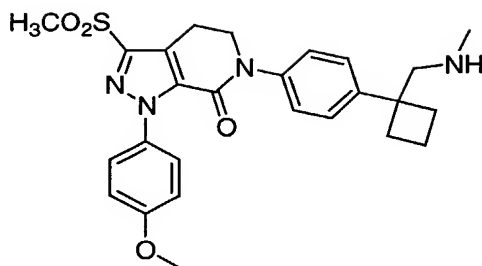
Following a procedure analogous to that of Example 25, the title compound was prepared. The product was purified by RP-prep LC-MS (35-98% CH₃CN/H₂O in a 10-min run). LC/MS
 (ESI⁺) 550.4 (M+H)⁺, t_R = 2.36 min.

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Example 59

1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclobutyl}phenyl)-3-(methanesulfonyl)-1,4,5,6-tetrahydro 7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt

25



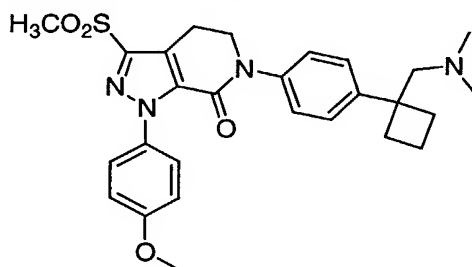
Following a procedure analogous to that used for Example 48, the title compound was prepared. It was then purified by prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run, t_R = 4.04

5 min). LC/MS (ESI⁺) 495.4 (M+H)⁺. ¹H NMR (acetone-*d*₆) δ 7.53 (d, J = 8.8 Hz, 4H), 7.32 (m, 4H), 7.00 (d, J = 9.1 Hz, 2H), 4.14 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.47 (br, s, 2H), 3.27 (m, 5H), 2.61 (br, s, 3H), 2.48-1.85 (m, 6H) ppm.

10

Example 60

6-(4-{1-[(dimethylamino)methyl]cyclobutyl}phenyl)-1-(4-methoxyphenyl)-3-(methanesulfonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



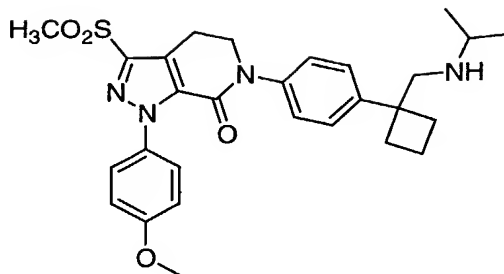
15

Following a procedure analogous to that used in Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 509.4 (M+H)⁺, t_R = 4.15 min.

20

Example 61

6-(4-{1-[(isopropylamino)methyl]cyclobutyl}phenyl)-1-(4-methoxyphenyl)-3-(methanesulfonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



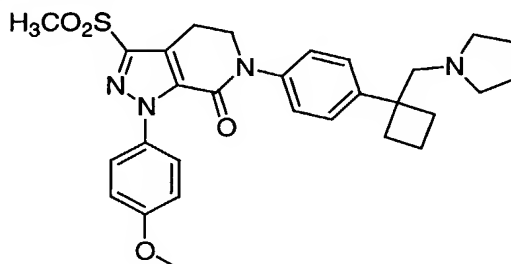
Following a procedure analogous to that used in Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS

5 (ESI⁺) 523.4 (M+H)⁺, t_R = 4.27 min. ¹H NMR (acetone-*d*₆) δ 7.53 (d, J = 9.1 Hz, 4H), 7.36 (AA'BB', J = 8.4 Hz, 4H), 7.00 (d, J = 8.8 Hz, 2H), 4.16 (t, J = 6.6 Hz, 2H), 3.84 (s, 3H), 3.52 (br, s, 2H), 3.27 (m, 5H), 2.81 (m, 1H), 2.42 (m, 4H), 2.04-1.94 (m, 2H), 1.17 (d, J = 7.3 Hz, 6H) ppm.

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Example 62

1-(4-methoxyphenyl)-3-(methylsulfonyl)-6-{4-[1-(1-pyrrolidin-1-ylmethyl)cyclobutyl]phenyl}-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



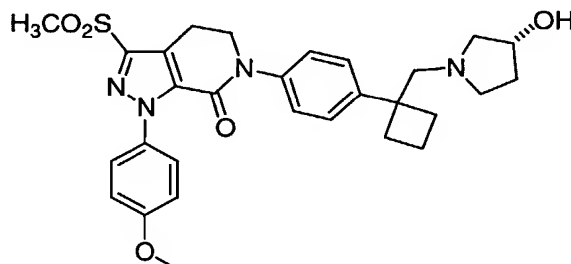
15

Following a procedure analogous to that used in Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (15-70% CH₃CN/H₂O in a 10-min run). LC/MS

20 (ESI⁺) 535.4 (M+H)⁺, t_R = 4.74 min. ¹H NMR (acetone-*d*₆) δ 7.53 (d, J = 8.8 Hz, 2H), 7.41 (AA'BB', J = 8.8 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 4.18 (t, J = 6.6 Hz, 2H), 4.14 (m, 4H), 3.83 (m, 5H), 3.27 (m, 5H), 2.46 (m, 4H), 2.09-1.85 (m, 6H) ppm.

Example 63

**6-[4-(1-[(3*R*)-3-hydroxy-1-pyrrolidinyl]methyl)cyclobutyl]phenyl]-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-
 5 c]pyridin-7-one, trifluoroacetic acid salt**

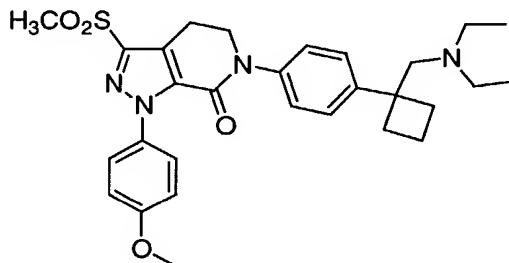


Following a procedure analogous to that used in Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS
 10 (ESI⁺) 551.4 (M+H)⁺, *t_R* = 4.06 min. ¹H NMR (acetone-*d*₆) δ 7.53 (d, *J* = 9.1 Hz, 2H), 7.40 (m, 4H), 6.99 (d, *J* = 9.1 Hz, 2H), 4.30 (m, 1H), 4.18 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 3.78 (m, 2H), 3.49 (m, 2H), 3.27 (m, 5H), 2.82 (m, 2H), 2.46 (m, 6H), 2.10-1.81 (m, 2H) ppm.

15

Example 64

6-(4-{1-[(diethylamino)methyl]cyclobutyl}phenyl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



20

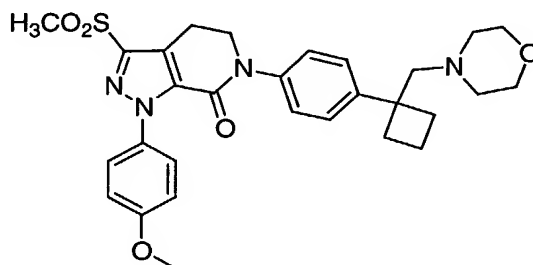
Following a procedure analogous to that used in Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS
 25 (ESI⁺) 537.4 (M+H)⁺, *t_R* = 4.62 min. ¹H NMR (acetone-*d*₆) δ 7.53 (d, *J* = 8.8 Hz, 4H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.00

(d, $J = 9.2$ Hz, 2H), 4.18 (t, $J = 6.6$ Hz, 2H), 3.83 (s, 3H), 3.74 (m, 2H), 3.27 (s+t, 5H), 3.03 (m, 4H), 2.49 (t, $J = 7.5$ Hz, 4H), 2.09–1.89 (m, 2H), 1.19 (t, $J = 7.4$ Hz, 6H) ppm.

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Example 65

1-(4-methoxyphenyl)-3-(methylsulfonyl)-6-{4-[1-(4-morpholinylmethyl)cyclobutyl]phenyl}-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one, trifluoroacetic acid salt



10

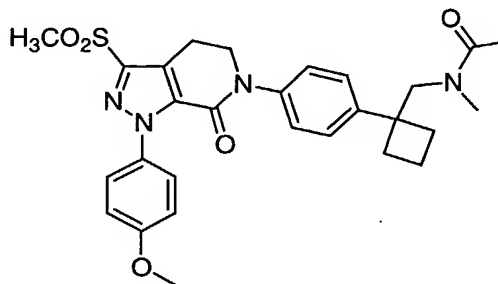
Following a procedure analogous to that used in Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5–98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 551.4 (M+H)⁺, $t_R = 4.12$ min. ¹H NMR (acetone-*d*₆) δ 7.53 (d, $J = 8.8$ Hz, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 7.37 (d, $J = 8.8$ Hz, 2H), 7.00 (d, $J = 9.1$ Hz, 2H), 4.17 (t, $J = 6.6$ Hz, 2H), 3.83 (s, 3H), 3.74 (m, 10H), 3.27 (m, 5H), 2.46 (m, 4H), 2.10–1.84 (m, 2H) ppm.

15

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Example 66

N-[(1-{4-[1-(4-methoxyphenyl)-3-(methylsulfonyl)-7-oxo-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl}cyclopropyl)methyl]-N-methylacetamide



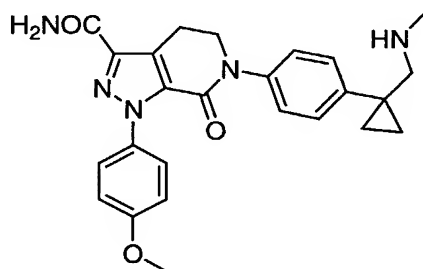
Following a procedure analogous to that of Example 21, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). ESI, LC/MS (ESI⁺) 551.4 (M+H)⁺, *t*_R = 4.12 min.

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Example 67

1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide, trifluoroacetic acid salt

10



Part A. 4-Iodophenylcyclopropyl acetic acid (1.93 g, 6.70 mmol) and 1-(4-methoxyphenyl)-3-(ethoxycarbonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (1.41 g, 4.46 mmol) were stirred in DMSO (4 mL) under N₂. K₂CO₃ (1.84 g, 13.33 mmol, 3.0 eq) was added followed by the addition of 1,10-phenanthroline (0.15 g, 20 mol%) and CuI (0.16 g, 20mol%). The resulting mixture was stirred at 110°C overnight. LC-MS showed completion of the reaction. EtOAc was added to the cooled solution. It was acidified with 1*N* HCl, and the organic layer was washed with H₂O, and brine, dried over MgSO₄, filtered, and concentrated to afford 1-{4-[3-(ethoxycarbonyl)-1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropanecarboxylic acid (1.54 g, yield: 72.6%). LC/MS (ESI⁺) 476.4 (M+H)⁺, *t*_R = 2.58 min (10-90% CH₃CN/H₂O in a 4-min run).

Part B. The product from part B (1.43 g, 3.01 mmol) was stirred in THF (13 mL) at 0°C under N₂. Et₃N (0.63 mL, 4.32

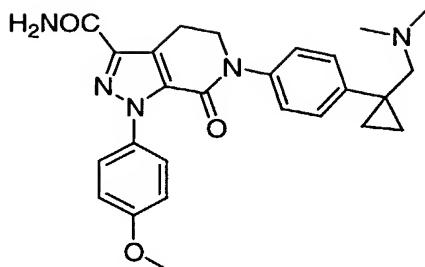
mmol, 1.5 eq) was added followed by dropwise addition of ClCOOEt (0.37 mL, 4.16 mmol, 1.3 eq). The reaction mixture was then stirred at 0°C for 20 min. TLC showed completion of the reaction. The mixture was filtered, and rinsed with anhydrous THF. The THF filtrate (ca. 20 mL) was stirred at 0°C under N₂. MeOH (3 mL) was added followed by the addition of NaBH₄ (1.03 g, 27.10 mmol, 10 eq). The resulting mixture was stirred at 0°C for 15 min. Analytical LC-MS showed completion of the reaction. Sat'd Na₂SO₄ was then added. The mixture was extracted with EtOAc (2x). The organic layer was washed with H₂O (2x) and brine (2x), dried over Na₂SO₄, filtered, and concentrated to dryness to give 6-{4-[1-(hydroxymethyl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-(ethoxycarbonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (1.30 g, 99%). LC/MS (ESI⁺) 462.6 (M+H)⁺, t_R = 2.57 min (10-90% CH₃CN/H₂O in a 4-min run).

Part C. The product from part B (1.90 g, 4.12 mmol) was stirred in anhydrous CH₂Cl₂ (13 mL) at RT under N₂. NaOAc (1.01 g, 12.20 mmol, 3 eq) and molecular sieves (2.0 g) were added followed by the addition of PCC (1.78 g, 8.24 mmol, 2 eq). The resulting slurry was stirred at RT for 1.5 h. Analytical LC-MS showed completion of the reaction. The mixture was filtered, and rinsed with CH₂Cl₂. The filtrate was washed with H₂O (2x) and brine (2x), dried over Na₂SO₄, filtered, and concentrated to dryness to afford ethyl 6-[4-(1-formylcyclopropyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (1.90 g, yield: 100%). LC/MS (ESI⁺) 460.6 (M+H)⁺, t_R = 2.69 min (10-90% CH₃CN/H₂O in a 4-min run).

- Part D. The product from part C (250 mg, 0.55 mmol), methylamine hydrochloride (0.5 g, excess) were stirred in dichloroethane (15 mL) at RT under N₂. NaBH(OAc)₃ (1.03 g, 4.86 mmol) was added followed by addition of three drops of HOAc. The reaction mixture was stirred at RT for 1.5 h. Analytical LC-MS showed completion of the reaction. The mixture was quenched with H₂O, and extracted with EtOAc (2x). The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated to dryness to obtain crude ethyl 1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (109 mg, yield: 42%). LC/MS (ESI⁺) 475.4 (M+H)⁺, t_R = 2.08 min.
- Part E. The product from part D (50 mg, 0.105 mmol) was stirred in ethylene glycol (saturated with NH₃) in a capped Pyrex tube at 80°C for 4 h. After cooling, the mixture was diluted with MeOH, and purified by prep LC-MS (5-98% CH₃CN in H₂O in a 10-min run) to afford 1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (29 mg, yield: 60%). LC/MS (ESI⁺) 445.4 (M+H)⁺, t_R = 3.53 min. ¹H NMR (acetone-*d*₆) δ 7.49 (m, 4H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.97 (d, *J* = 9.1 Hz, 2H), 4.06 (t, *J* = 6.6 Hz, 2H), 3.82 (s, 3H), 3.32 (s, 2H), 3.24 (t, *J* = 6.6 Hz, 2H), 2.66 (s, 3H), 1.10 (m, 2H), 0.94 (m, 2H) ppm.

Example 68

- 6-(4-{1-[(dimethylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide, trifluoroacetic acid salt



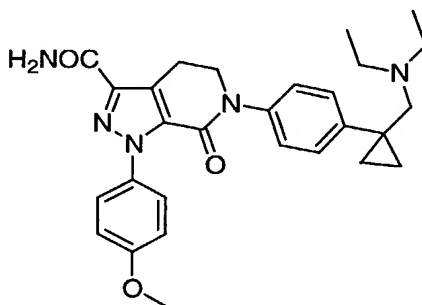
Following a procedure analogous to that used in Example 67, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS

(ESI⁺) 460.6 (M+H)⁺, t_R = 3.93 min. ¹H NMR (acetone-*d*₆) δ 7.52 (m, 4H), 7.33 (m, 2H), 6.97 (d, J = 9.2 Hz, 2H), 4.10 (t, J = 6.3 Hz, 2H), 3.82 (s, 3H), 3.52 (m, 2H), 3.26 (t, J = 6.3 Hz, 2H), 2.69 (m, 6H), 1.18 (m, 2H), 1.04 (m, 2H) ppm.

10

Example 69

6-(4-{1-[(diethylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide, trifluoroacetic acid salt



15

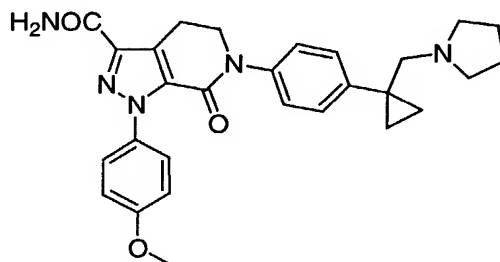
Following a procedure analogous to that used in Example 67, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS

(ESI⁺) 488.6 (M+H)⁺, t_R = 3.90 min. ¹H NMR (acetone-*d*₆) δ 7.57 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 9.1 Hz, 2H), 4.08 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.62 (m, 2H), 3.24 (m, 6H), 1.16 (m, 8H), 1.05 (m, 2H) ppm.

20

Example 70

1-(4-methoxyphenyl)-7-oxo-6-{4-[1-(1-pyrrolidinylmethyl)cyclopropyl]phenyl}-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide, trifluoroacetic acid salt

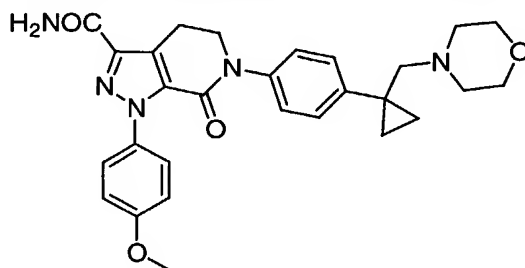


Following a procedure analogous to that used in Example 67, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS

(ESI⁺) 486.4 (M+H)⁺, t_R = 3.88 min. ¹H NMR (acetone-d₆) δ 7.52 (m, 2H), 7.32 (m, 4H), 6.99 (m, 2H), 4.09 (m, 2H), 3.82 (s, 3H), 3.56 (m, 6H), 3.26 (m, 2H), 1.91 (m, 4H), 1.13 (m, 2H), 0.98 (m, 2H) ppm.

Example 71

1-(4-methoxyphenyl)-6-{4-[1-(4-morpholinylmethyl)cyclopropyl]phenyl}-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide, trifluoroacetic acid salt



Following a procedure analogous to that used in Example 67, the title compound was prepared. It was then purified by prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run, t_R = 3.67 min). LC/MS (ESI⁺) 502.6 (M+H)⁺. ¹H NMR (acetone-d₆) δ 7.51 (d, J

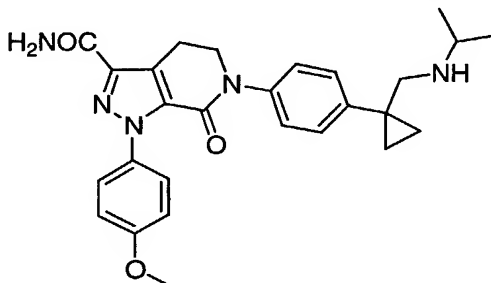
= 8.6 Hz, 4H), 7.34 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4

Hz, 4H), 6.95 (d, $J = 9.2$ Hz, 2H), 4.09 (t, $J = 6.6$ Hz, 2H), 3.82 (s, 3H), 3.48 (m, 6H), 3.26 (t, $J = 6.6$ Hz, 2H), 2.82 (m, 2H), 2.40 (m, 2H), 0.81 (m, 2H), 0.73 (m, 2H) ppm.

5

Example 72

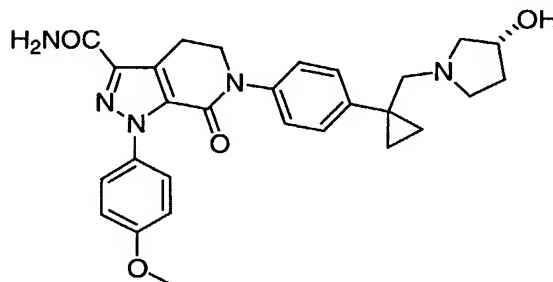
6-(4-{1-[(isopropylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide, trifluoroacetic acid salt



10 Following a procedure analogous to that used in Example 67, the title compound was prepared. It was then purified by prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run, $t_R = 4.18$ min). LC/MS (ESI⁺) 474.4 (M+H)⁺. ¹H NMR (acetone-*d*₆) δ 7.53 (m, 4H), 7.28 (d, $J = 8.1$ Hz, 2H), 6.97 (d, $J = 7.7$ Hz, 2H),
 15 4.08 (m, 2H), 3.82 (s, 3H), 3.35 (m, 3H), 3.25 (m, 2H), 1.27 (d, $J = 6.2$ Hz, 6H), 1.11 (m, 2H), 0.92 (m, 2H) ppm.

Example 73

20 **6-[4-(1-{[(3R)-3-hydroxy-1-pyrrolidinyl]methyl}cyclopropyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide, trifluoroacetic acid salt**



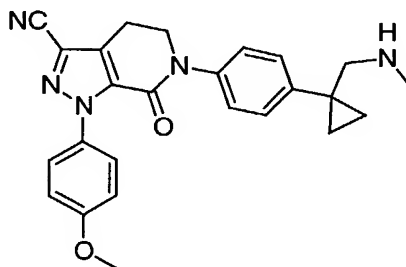
Following a procedure analogous to that used in Example 67, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 502.4 (M+H)⁺, t_R = 3.81 min.

5

Example 74

1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carbonitrile, trifluoroacetic acid salt

10



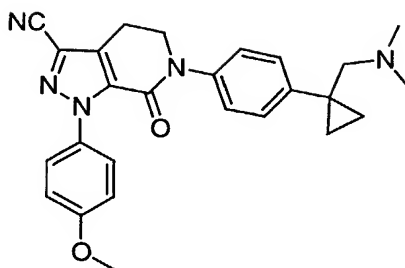
The product of Example 67 (15 mg) was stirred in DMF (0.5 mL) at RT in a capped vial. Two drops of thionyl chloride was added. The reaction was completed in 10 min. The mixture was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run) to give pure 1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carbonitrile (11 mg, yield: 76.2%). LC/MS (ESI⁺) 428.4 (M+H)⁺, t_R = 4.49 min.

20

Example 75

6-(4-{1-[(dimethylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carbonitrile, trifluoroacetic acid salt

25



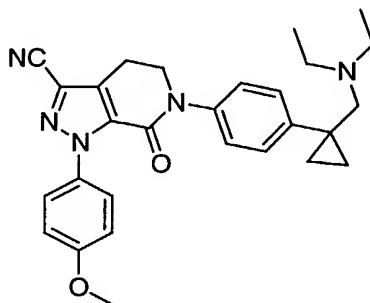
Following a procedure analogous to that used in Example 74, the title compound was prepared. It was then purified by prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run, t_R = 4.44 min).

5 LC/MS (ESI⁺) 442.6 (M+H)⁺. ¹H NMR (acetone-*d*₆) δ 7.53 (m, 4H), 7.33 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 9.2 Hz, 2H), 4.18 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.57 (s, 2H), 3.18 (t, J = 6.6 Hz, 2H), 2.78 (s, 6H), 1.16 (m, 2H), 1.06 (m, 2H) ppm.

10

Example 76

6-(4-{1-[(diethylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carbonitrile, trifluoroacetic acid salt



15

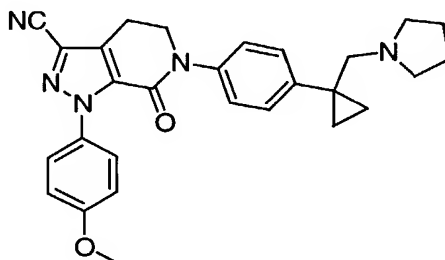
Following a procedure analogous to that used in Example 74, the title compound was prepared. It was then purified by prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run, t_R = 4.60 min).

16 LC/MS (ESI⁺) 470.6 (M+H)⁺. ¹H NMR (acetone-*d*₆) δ 7.58 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 9.1 Hz, 2H), 4.19 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.58-3.18 (m, 6H), 3.19 (t, J = 6.6 Hz, 2H), 1.18 (m, 8H), 1.06 (m, 2H) ppm.

20

Example 77

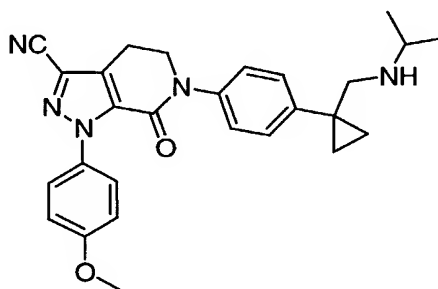
1-(4-methoxyphenyl)-7-oxo-6-(4-[1-(1-pyrrolidinylmethyl)cyclopropyl]phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carbonitrile, trifluoroacetic acid salt



Following a procedure analogous to that used in step F of Example 74, the title compound was prepared. LC/MS (ESI⁺) 468.4 (M+H)⁺, *t*_R = 4.49 min. ¹H NMR (acetone-*d*₆) δ 7.52 (d, *J* = 9.0 Hz, 2H), 7.44 (AA'BB', *J* = 8.6 Hz, 4H), 6.99 (d, *J* = 8.8 Hz, 2H), 4.18 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 3.59 (m, 2H), 3.19 (t, *J* = 6.6 Hz, 2H), 2.75 (m, 4H), 2.01 (m, 4H), 1.14 (m, 2H), 1.00 (m, 2H).

Example 78

6-(4-{1-[(isopropylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carbonitrile, trifluoroacetic acid salt



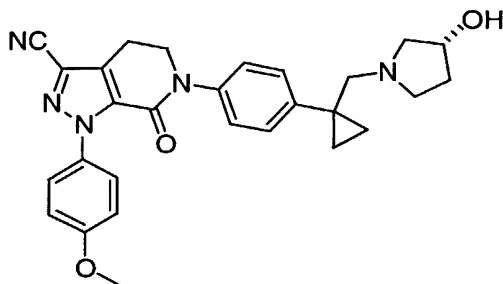
Following a procedure analogous to that used in Example 74, the title compound was prepared. It was then purified by prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run, *t*_R = 4.57 min). LC/MS (ESI⁺) 456.6 (M+H)⁺. ¹H NMR (acetone-*d*₆) δ 7.53 (m, 4H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 9.1 Hz, 2H),

4.17 (t, $J = 6.6$ Hz, 2H), 3.83 (s, 3H), 3.19 (t, $J = 6.6$ Hz, 2H), 3.17 (m, 3H), 1.28 (d, $J = 6.6$ Hz, 6H), 1.13 (m, 2H), 0.93 (m, 2H) ppm.

5

Example 79

6-[4-(1-[(3*R*)-3-hydroxy-1-pyrrolidinyl]methyl)cyclopropyl]phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt



10

Following a procedure analogous to that used in Example 74, the title compound was prepared. It was then purified by prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run, $t_R = 4.34$ min).

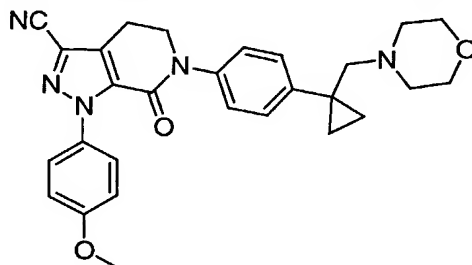
LC/MS (ESI⁺) 484.4 (M+H)⁺. ¹H NMR (acetone-*d*₆) δ 7.53 (m, 4H), 7.35 (d, $J = 8.4$ Hz, 2H), 6.99 (d, $J = 9.2$ Hz, 2H), 4.19 (t, $J = 6.6$ Hz, 2H), 3.83 (s, 3H), 3.62 (m, 5H), 3.19 (t, $J = 6.6$ Hz, 2H), 2.91 (m, 2H), 1.85 (m, 2H), 1.18 (m, 2H), 1.01 (m, 2H) ppm.

15

20

Example 80

1-(4-methoxyphenyl)-6-{4-[1-(4-morpholinylmethyl)cyclopropyl]phenyl}-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt



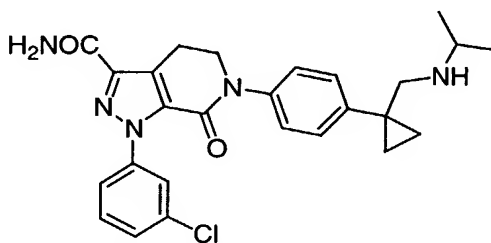
25

Following a procedure analogous to that used in Example 67, the title compound was prepared. It was then purified by prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run, *t_R* = 4.46 min).

LC/MS (ESI⁺) 484.6 (M+H)⁺. ¹H NMR (acetone-*d*₆) δ 7.52 (m, 4H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 9.2 Hz, 2H), 4.17 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 3.47 (m, 7H), 3.62 (s, 2H), 3.49 (m, 2H), 3.17 (t, *J* = 6.6 Hz, 2H), 3.07 (m, 2H), 1.17 (m, 2H), 1.06 (m, 2H) ppm.

Example 81

1-(3-chlorophenyl)-6-{4-[1-(isopropylamino)methyl)cyclopropyl]phenyl}-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide



Part A. 1-(3-Chlorophenyl)-3-(ethoxycarbonyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (1.14 g, 3.57 mmol) and 4-iodophenylcyclopropyl acetic acid (1.13 g, 1.1 eq) were stirred in DMSO (4 mL) under N₂. K₂CO₃ (1.48 g, mmol, 3 eq) was added, followed by the addition of 1,10-phenanthroline (0.13 g, 20 mol%) and CuI (0.14 g, 20 mol%). The resulting mixture was stirred at 130°C overnight. LC-MS showed completion of the reaction. EtOAc was added to the cooled solution. It was washed with 1N HCl, H₂O, and brine; dried over MgSO₄; filtered; and concentrated in vacuo to give almost pure 1-{4-[1-(3-chlorophenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropanecarboxylic acid (0.87 g, yield: 51%). LC/MS (ESI⁺) 480.4 (M+H)⁺.

Part B. The product from Part A (0.54 g, 1.13 mmol) was stirred in THF (6 mL) at 0°C under N₂. Et₃N (0.24 mL, 1.5 eq) was added, followed by dropwise addition of ClCOOEt (0.14 mL, 1.3 eq). The reaction mixture was then stirred at 0°C for 1 h. TLC showed the completion of the reaction. The mixture was filtered through a filter funnel and rinsed with anhydrous THF. The THF filtrate (ca. 10 mL) was stirred at 0°C under N₂. NaBH₄ (0.52 g, 10 eq) was added, followed by the addition of MeOH (2.5 mL). The resulting mixture was stirred at 0°C. Analytical LC-MS showed completion of the reaction. Sat'd Na₂SO₄ was then added. The mixture was extracted with EtOAc (2x). The organic layer was washed with H₂O (2x) and brine (2x), dried over Na₂SO₄, filtered, and concentrated to dryness to give 1-(3-chlorophenyl)-6-{4-[1-(hydroxymethyl)cyclopropyl]phenyl}-3-(ethoxycarbonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (0.31 g, yield: 52.4%). LC/MS (ESI⁺) 466.4 (M+H)⁺.

Part C. The product from Part B (0.31 g, 0.22 mmol) was stirred in anhydrous CH₂Cl₂ (5 mL) at RT under N₂. NaOAc (0.16 g, 1.95 mmol) and molecular sieves (0.5 g) were added, followed by the addition of PCC (0.29 g, 1.34 mmol). The resulting slurry was stirred at RT for 1.5h. Analytical LC-MS showed completion of the reaction. The mixture was filtered through Celite, and rinsed with CH₂Cl₂. The filtrate was washed with H₂O (2x), brine (2x), dried over Na₂SO₄, filtered, and concentrated to dryness to give almost pure 1-(3-chlorophenyl)-6-[4-(1-(formylcyclopropyl)phenyl]-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester (0.20 g, yield: 87.4%). LC/MS (ESI⁺) 464.4 (M+H)⁺.

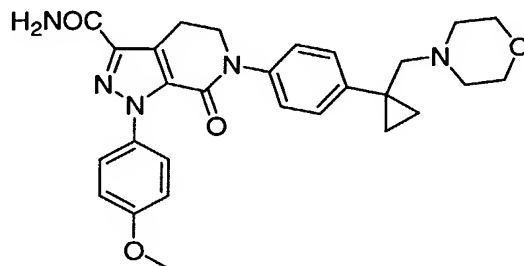
Part D. The product from Part C (100 mg) and isopropyl amine (0.1 mL, excess) were stirred in dichloroethane (1

mL) in a capped vial. $\text{NaBH}(\text{OAc})_3$ (200 mg) was added, followed by addition of one drop of HOAc. The reaction mixture was stirred at RT for 1.5 h. Analytical LC-MS showed completion of the reaction. The mixture was
5 evaporated, and dissolved in aqueous MeOH. It was then purified by prep LC-MS (5-98% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ in a 10-min run) to obtain pure 1-(3-chlorophenyl)-6-{4-[1-(isopropylamino)methyl)cyclopropyl]phenyl}-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (60 mg,
10 yield: 55%). LC/MS (ESI^+) 507.4 ($\text{M}+\text{H}^+$), $t_R = 4.68$ min.

Part E. The product from part D (60 mg) was stirred in ethylene glycol (saturated with NH_3) in a capped Pyrex tube at 80°C for 4 h. After cooling, the mixture was diluted
15 with MeOH and purified by prep LC-MS (5-98% CH_3CN in H_2O in a 10-min run) to afford the title compound (35 mg, yield: 62%). LC/MS (ESI^+) 478.4 ($\text{M}+\text{H}^+$), $t_R = 4.34$ min. ^1H NMR (acetone- d_6) δ 7.74 (s, 1H), 7.63 (m, 1H), 7.45 (m, 4H), 7.30 (d, $J = 8.4$ Hz, 2H), 4.11 (t, $J = 6.6$ Hz, 2H), 3.44
20 (m, 1H), 3.38 (m, 2H), 3.26 (t, $J = 6.6$ Hz, 2H), 1.29 (d, $J = 6.6$ Hz, 6H), 1.12 (m, 2H), 0.94 (m, 2H) ppm.

Example 82

25 **1-(3-chlorophenyl)-6-{4-[1-(4-morpholinylmethyl)cyclopropyl]phenyl}-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide, trifluoroacetic acid salt**

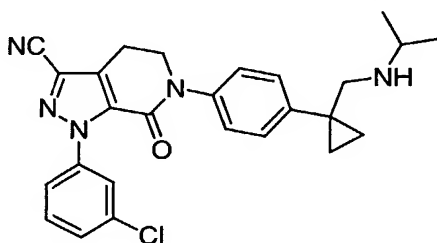


Following a procedure analogous to that used in Example 81,
30 the title compound was prepared. The product was purified

by prep LC-MS (5-98% CH₃CN in H₂O in a 10-min run). LC/MS (ESI⁺) 506.6 (M+H)⁺, *t*_R = 4.57 min. ¹H NMR (acetone-*d*₆) δ 7.73 (s, 1H), 7.63 (m, 1H), 7.47 (m, 4H), 7.29 (m, 2H), 4.09 (t, *J* = 6.6 Hz, 2H), 3.74 (m, 4H), 3.53 (m, 2H), 3.27 (m, 2H), 3.07 (m, 4H), 1.07 (m, 2H), 1.00 (m, 2H) ppm.

Example 83

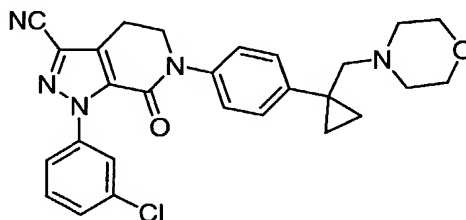
6-(4-{1-[(isopropylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt



Following a procedure analogous to that used in step F of Example 74, the title compound was prepared. It was then purified by prep LC-MS (35-98% CH₃CN/H₂O in a 10-min run, *t*_R = 2.78 min). LC/MS (ESI⁺) 460.6 (M+H)⁺. ¹H NMR (acetone-*d*₆) δ 7.75 (s, 1H), 7.63 (m, 1H), 7.53 (m, 4H), 7.31 (d, *J* = 8.8 Hz, 2H), 4.19 (t, *J* = 6.6 Hz, 2H), 3.48 (m, 1H), 3.41 (m, 2H), 3.21 (t, *J* = 6.6 Hz, 2H), 1.29 (d, *J* = 6.3 Hz, 6H), 1.14 (m, 2H), 0.95 (m, 2H) ppm.

Example 84

1-(4-methoxyphenyl)-6-{4-[1-(4-morpholinylmethyl)cyclopropyl]phenyl}-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carbonitrile, trifluoroacetic acid salt



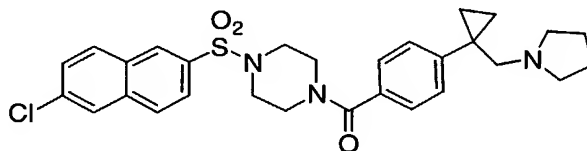
Following a procedure analogous to that used in Example 74, the title compound was prepared. It was then purified by prep LC-MS (35-98% CH₃CN/H₂O in a 10-min run, *t_R* = 2.80

min). LC/MS (ESI⁺) 488.6 (M+H)⁺. ¹H NMR (acetone-*d*₆) δ

5 7.73 (s, 1H), 7.62 (m, 1H), 7.54 (m, 4H), 7.34 (m, 2H), 4.19 (m, 2H), 3.83 (m, 8H), 3.61 (m, 2H), 3.19 (m, 2H), 1.17 (m, 2H), 1.05 (m, 2H) ppm.

Example 85

10 **1-[(6-chloro-2-naphthyl)sulfonyl]-4-{4-[1-(1-pyrrolidinylmethyl)cyclopropyl]benzoyl}piperazine**



Part A. 1-(4-Iodophenyl)cyclopropane carboxylic acid (0.64 g, 2.25 mmol) was stirred in THF (10 mL) at 0°C under N₂.

15 Et₃N (0.47 mL, 3.37 mmol) was added, followed by dropwise addition of ClCO₂Et (0.28 mL, 2.93 mmol). The reaction mixture was then stirred at 0°C for 30 min. TLC showed the completion of the reaction. The mixture was filtered through a filter funnel and rinsed with anhydrous THF. The THF filtrate (ca.15 mL) was stirred at 0°C under N₂. NaBH₄ (0.41 g, 10.8 mmol) was added, followed by addition of MeOH (3 mL). The resulting mixture was stirred at 0°C for 30 min. Analytical LC-MS showed completion of the reaction. Sat'd Na₂SO₄ was then added. The mixture was extracted with 25 EtOAc (2x). The organic layer was washed with H₂O (2x) and brine (2x), dried over Na₂SO₄, filtered, and concentrated to dryness. The resulting alcohol was stirred in anhydrous CH₂Cl₂ (10 mL) at RT under N₂. NaOAc (0.42 g, 5.12 mmol) and molecular sieves (4Å, 0.75 g) were added, followed by 30 the addition of PCC (0.83 g, 3.84 mmol). The resulting slurry was stirred at RT for 1.5 h. Analytical LC-MS showed completion of the reaction. The mixture was

filtered through Celite, and rinsed with CH_2Cl_2 . The filtrate was washed with H_2O (2x) and brine (2x), dried over Na_2SO_4 , filtered, and concentrated in vacuo to give almost pure 4-iodophenylcyclopropanecarbaldehyde. This
5 aldehyde and pyrrolidine (0.37 mmol) were stirred in dichloroethane (6 mL) at RT under N_2 . $\text{NaBH}(\text{OAc})_3$ (1.37 mg, mmol) was added, followed by addition of several drops of HOAc. The reaction mixture was stirred at RT for 20 min. Analytical LC-MS showed completion of the reaction. H_2O
10 was added. The mixture was extracted with EtOAc; and the organic extracts were washed with H_2O (2x) and brine (2x), dried over Na_2SO_4 , filtered, and concentrated to dryness to give almost pure 1-([1-(4-iodophenyl)cyclopropyl]methyl)pyrrolidine (0.41 g, yield %
15 for 3 steps). LC/MS (ESI^+) 328.2 ($\text{M}+\text{H}^+$) (10-90% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ in a 4-min run, $t_R = 1.77$ min).

Part B. The product from part A (0.40 g, 1.24 mmol), KOAc (0.61 g, 5.0 eq), $\text{Pd}(\text{OAc})_2$ (0.03 g, 0.1 eq), and dppf (0.14
20 g, 0.2 eq) were stirred in DMF (3 mL) at RT. The mixture was degassed twice and purged with CO. The mixture was heated at 60°C under CO atmosphere with a balloon for 2.5 h. LS-MS showed completion of the reaction. After cooling, H_2O was added. The mixture was extracted with
25 EtOAc (2x). The aqueous layer was then acidified, and concentrated to dryness. MeOH was added, and filtered off inorganic salts. The filtrate was concentrated and vacuum dried to give almost pure 4-[1-(1-pyrrolidinylmethyl)cyclopropyl]benzoic acid (0.32 g, yield:
30 96%). LC/MS (ESI^+) 246.4 ($\text{M}+\text{H}^+$) (10-90% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ in a 4-min run, $t_R = 1.32$ min).

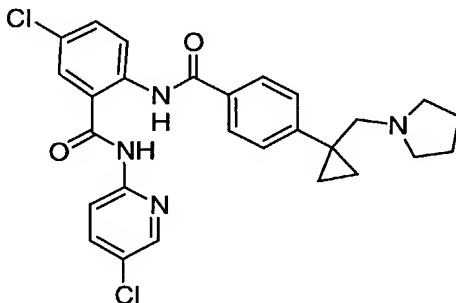
Part C. The product of part B (0.41 g, 1.68 mmol) was stirred in CH_2Cl_2 (10 mL) at RT under N_2 . $(\text{COCl})_2$ (0.5 mL)

was added, followed by the addition of one drop of DMF. The mixture was stirred at RT for 1 h. The solvent was evaporated and dried in vacuo. The resulting acid chloride (0.16 g, 0.61 mmol) was dissolved in CH₂Cl₂ (10 mL), 1-[(6-chloro-2-naphthyl)sulfonyl]piperazine (0.21 g, 0.61 mmol) was added, followed by the addition of DIEA (0.21 mL, 1.21 mmol). The resulting mixture was stirred at RT for 20 min. Analytical LC-MS showed completion of the reaction. The solvent was evaporated. The residue was dissolve in MeOH, and purified by RP Prep LC-MS (5-98% CH₃CN in H₂O in a 10-min run) to give pure title compound (210 mg, yield: 64.1%). It was then purified by prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run, t_R = 4.71 min). LC/MS (ESI⁺) 538.4 (M+H)⁺.

15

Example 86

5-chloro-N-(5-chloro-2-pyridinyl)-2-({4-[1-(1-pyrrolidinylmethyl)cyclopropyl]benzoyl}amino)benzamide, trifluoroacetic acid salt



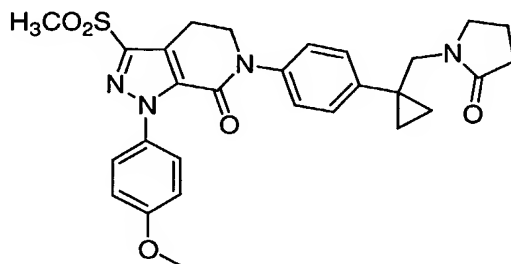
20 Part A. The product from Part B of Example 85 (0.16 g, 0.65 mmol) was stirred in CH₂Cl₂ (5 mL) at RT under N₂. (COCl)₂ (0.2 mL) was added. The mixture was stirred at RT for 1 h. The solvent was evaporated and dried in vacuo. The resulting acid chloride was dissolved in CH₂Cl₂ (6 mL),
25 2-amino-5-chlorobenzoic acid methyl ester (0.16 g, 0.86 mmol) was added, followed by the addition of DIEA (0.30 mL). The resulting mixture was stirred at RT for 2 h. Analytical LC-MS showed completion of the reaction. The solvent was evaporated. The residue was dissolve in EtOAc,

washed with H₂O, brine, dried over MgSO₄, and concentrated to give methyl 5-chloro-2-({4-[1-(1-pyrrolidinylmethyl)cyclopropyl]benzoyl}amino)benzoate (55 mg, yield: 21%). LC/MS (ESI⁺) 413.4 (M+H)⁺, t_R = 2.19 min
 5 (10-90% CH₃CN/H₂O in a 4-min run).

Part B. The product from Part A (30 mg) and 5-chloro-2-aminopyridine (14 mg) were stirred in CH₂Cl₂ (1 mL) at RT under N₂. Me₃Al in toluene (0.45 mL, 0.23 mmol) was added
 10 dropwise. The resulting solution was stirred at RT for 1h and at reflux for 2h. The solvent was evaporated after cooling. The residue was dissolved in MeOH, and purified by LC-MS (5-98% CH₃CN in H₂O in a 10-min run) to give pure
 15 5-chloro-N-(5-chloro-2-pyridinyl)-2-({4-[1-(1-pyrrolidinylmethyl)cyclopropyl]benzoyl}amino)benzamide (6 mg, yield: 16%). LC/MS (ESI⁺) 509.2 (M+H)⁺, t_R = 2.21 min (10-90% CH₃CN/H₂O in a 4-min run).

Example 87

20 **1-(4-Methoxyphenyl)-3-methanesulfonyl-6-{4-[1-(2-oxo-pyrrolidin-1-ylmethyl)cyclopropyl]phenyl}-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one**



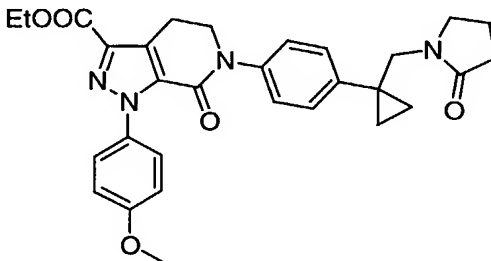
Part A. 1-(1-Bromomethylcyclopropyl)-4-iodobenzene (2.0 g, 5.97 mmol) and NaN₃ (1.0 g, 15.38 mmol, 2.6 eq) were
 25 stirred in DMF (10 mL) overnight. Analytical LC-MS showed completion of the reaction. EtOAc was added to the solution. The mixture was washed with H₂O and brine, dried over MgSO₄, and concentrated to give 1-(1-azidomethyl-
 30 cyclopropyl)-4-iodobenzene (1.43 g, yield: 80%). The azide

- (1.40 g, 4.68 mmol) and PPh_3 (1.84 g, 7.02 mmol, 1.5 eq) were stirred in THF (10 mL) at RT for 40 min. H_2O (2 mL) was added, and the solution was stirred at 50°C for 6h. LC-MS showed completion of the reaction. The mixture was
5 extracted with Et_2O (2x). The aqueous layer was basified with 50% NaOH, extracted with CH_2Cl_2 (2x), washed with H_2O , brine, dried over MgSO_4 , and concentrated to give 1-(4-iodophenyl)cyclopropyl methylamine (0.98 g, yield: 75%).
- 10 Part B. The product from Part A (0.36 g, 1.31 mmol) was stirred in dry CH_2Cl_2 (10 mL) at RT. NaOH (0.16 g, 3.93 mmol, 3 eq) was added, followed by the addition of 4-chlorobutyryl chloride (0.16 mL, 1.42 mmol). The reaction mixture was stirred at RT for 1h. It was washed with H_2O
15 and brine, dried over MgSO_4 , and concentrated to dryness. The residue was dissolved in THF (10 mL). K-O-tBu (0.29 g, 2.62 mmol) was added as one single portion. The mixture was stirred at 0°C under N_2 for 1h. LC-MS showed completion of the reaction. EtOAc was added. It was washed with H_2O
20 and brine, dried over MgSO_4 , and concentrated to produce 1-[1-(4-iodophenyl)cyclopropylmethyl]-pyrrolidin-2-one (0.36 g, yield: 86%). LC/MS (ESI^+) 342.0 ($\text{M}+\text{H}^+$), $t_R = 2.86$ min (10-90% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ in a 4-min run).
- 25 Part C. The product from Part B (0.18 g, 0.56 mmol) and 1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (0.16 g, 0.47 mmol) were stirred in DMSO (1 mL) under N_2 . K_2CO_3 (0.20 g, 1.44 mmol) was added, followed by the addition of CuI (0.030 g, 20
30 mol%) and 1,10-phenanthroline (0.028 g, 20 mol%). The resulting mixture was heated at 120°C overnight. After cooling, it was extracted with EtOAc (2x), washed with H_2O and brine, dried over MgSO_4 , filtered, and concentrated to dryness. The residue was purified by flash column

chromatography (silica gel, CH₂Cl₂:EtOAc = 1:1, then EtOAc) to give the desired compound (83 mg, yield: 25%). LC/MS (ESI⁺) 535.2 (M+H)⁺, t_R = 3.45 min (10-90% CH₃CN/H₂O in a 6-min run). ¹H NMR (CDCl₃) δ 7.45 (d, J = 8.8 Hz, 2H), 7.25 (AA'BB', J = 8.6 Hz, 4H), 6.91 (d, J = 9.2 Hz, 2H), 4.10 (t, J = 6.6 Hz, 2H), 3.80 (s, 3H), 3.68 (s, 2H), 3.46 (m, 2H), 3.29 (m, 3H), 3.23 (t, J = 6.6 Hz, 2H), 2.25 (m, 2H), 1.86 (m, 2H), 0.86 (m, 4H) ppm.

Example 88

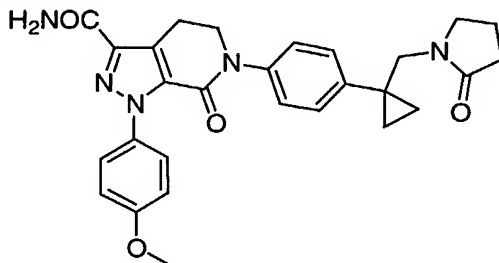
1-(4-Methoxyphenyl)-7-oxo-6-{4-[1-(2-oxo-pyrrolidin-1-ylmethyl)cyclopropyl]phenyl}-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester



Following a procedure analogous to that used for the preparation of Example 87, the title compound was prepared. The product was purified by silica gel column chromatography. LC/MS (ESI⁺) 529.4 (M+H)⁺, t_R = 3.14 min (25-90% CH₃CN/H₂O in a 6-min run).

Example 89

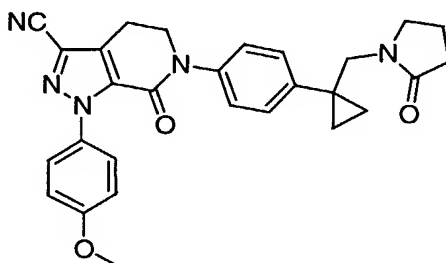
1-(4-Methoxyphenyl)-7-oxo-6-{4-[1-(2-oxo-pyrrolidin-1-ylmethyl)cyclopropyl]phenyl}-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide



Following a procedure analogous to that used for the preparation of Example 67, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 500.2 (M+H)⁺, t_R = 3.28 min
5 (10-90% CH₃CN/H₂O in a 6-min run).

Example 90

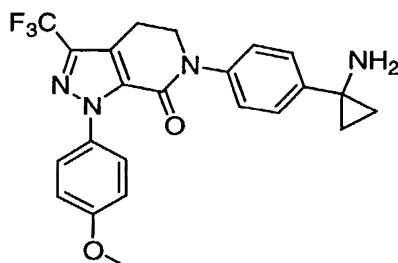
1- (4-Methoxyphenyl) -7-oxo-6- {4- [1- (2-oxo-pyrrolidin-1-ylmethyl)cyclopropyl]phenyl} -4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carbonitrile
10



Following a procedure analogous to that used for the preparation of Example 74, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). Analytical LC/MS (ESI⁺) 482.4 (M+H)⁺, t_R = 2.63 min (35-95% CH₃CN/H₂O in a 6-min run).
15

Example 91

6- [4- (1-Aminocyclopropyl)phenyl] -1- (4-methoxyphenyl) -3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridine-7-one, trifluoroacetic acid salt
20

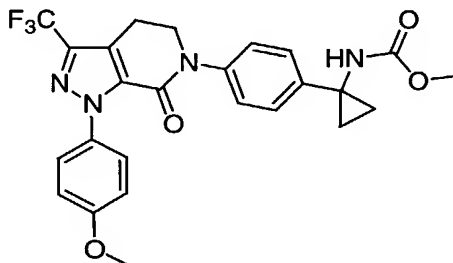


The product of Part D in Example 1 (ca. 0.50 g) was stirred in dry toluene at RT. DPPA (0.25 mL) was added, followed
25 by the addition of Et₃N (0.35 mL). The resulting mixture

was stirred at 100°C for 3h. After cooling to RT, 8N HCl (10 mL) was added. The resulting mixture was heated at 100°C overnight. The cooled mixture was extracted with Et₂O (2x). The aqueous layer was basified with 50% NaOH. The mixture was extract with chloroform (2x). The organics were washed with H₂O and brine, dried over MgSO₄, and concentrated to dryness. The residue was dissolved in MeOH, and purified by prep LC/MC (5-98% CH₃CN/H₂O in a 10-min run) to give the desired product. Analytical LC/MS (ESI⁺) 443.2 (M+H)⁺, *t_R* = 2.69 min (35-95% CH₃CN/H₂O in a 6-min run).

Example 92

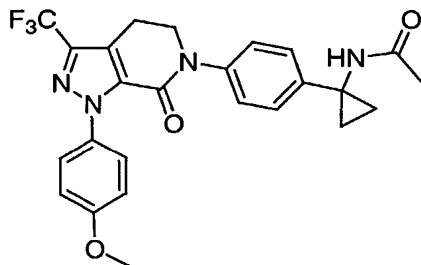
(1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)-carbamic acid methyl ester



Following a procedure analogous to that used for the preparation of Example 91, the title compound was prepared by using MeOH instead of conc. HCl as the solvent. Silica gel purification yielded the pure desired product. LC/MS (ESI⁺) 501.6 (M+H)⁺, *t_R* = 3.19 min (35-95% CH₃CN/H₂O in a 6-min run). ¹H NMR (CDCl₃) δ 7.46 (d, *J* = 8.8 Hz, 2H), 7.24 (m, 4H), 6.91 (d, *J* = 9.2 Hz, 2H), 4.12 (t, *J* = 6.6 Hz, 2H), 3.81 (s, 3H), 3.64 (s, 2H), 3.14 (t, *J* = 6.6 Hz, 2H), 1.22 (m, 4H) ppm.

Example 93

***N*-(1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-cyclopropyl)-acetamide**



5

Following a procedure analogous to that used for the preparation of Example 21, the title compound was prepared. Silica gel purification yielded the pure desired product.

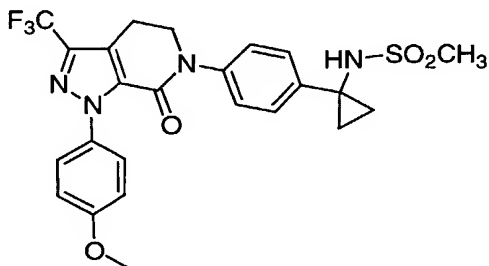
LC/MS (ESI⁺) 485.2 (M+H)⁺, *t*_R = 3.06 min (35-95% CH₃CN/H₂O

10 in a 6-min run). ¹H NMR (CDCl₃) δ 7.46 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.94 (AA'BB', *J* = 9.1 Hz, 4H), 4.09 (m, 2H), 3.81 (m, 2H), 3.14 (t, *J* = 6.6 Hz, 2H), 2.38 (s, 3H), 1.57 (m, 2H), 1.40 (m, 2H) ppm.

15

Example 94

***N*-(1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-cyclopropyl)-methanesulfonamide**



20 Silica gel purification yielded the pure desired product.

LC/MS (ESI⁺) 521.2 (M+H)⁺, *t*_R = 3.14 min (35-95% CH₃CN/H₂O

in a 6-min run). ¹H NMR (CDCl₃) δ 7.46 (d, *J* = 9.2 Hz, 2H),

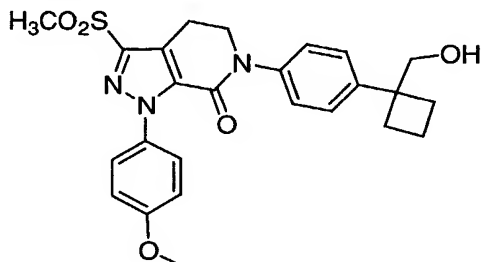
7.35 (AA'BB', *J* = 8.8 Hz, 4H), 6.92 (d, *J* = 8.8 Hz, 2H),

5.19 (s, 1H), 4.13 (t, *J* = 6.6 Hz, 2H), 3.81 (s, 3H), 3.16

25 (t, *J* = 6.6 Hz, 2H), 1.26 (m, 2H), 1.18 (m, 2H) ppm.

Example 95

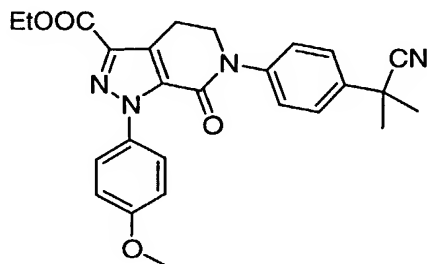
6-[4-(1-Hydroxymethylcyclopropyl)phenyl]-3-(methanesulfonyl)-1-(4-methoxyphenyl)-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one



Following a procedure analogous to that used for the preparation of product of Part C in Example 48, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH₃CN/H₂O in a 10-min run). LC/MS (ESI⁺) 481.4 (M+H)⁺, *t_R* = 5.51 min. ¹H NMR (acetone-*d*₆) δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.14 (t, *J* = 6.6 Hz, 2H), 3.83 (m, 4H), 3.63 (s, 2H), 3.27 (t, *J* = 6.6 Hz, 2H), 3.26 (s, 3H), 2.02 (m, 4H), 1.81 (m, 2H) ppm.

Example 96

Ethyl 6-[4-(cyano-dimethyl-methyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate



Part A. To 4-iodobenzylbromide (25 g, 84 mmol) in boiling EtOH (100 mL) was added potassium cyanide (8.2 g, 126 mmol) through the condenser. The reaction was heated 24h, then

cooled and EtOH removed. The aqueous layer was extracted with EtOAc and dried (Na_2SO_4) to afford crude 4-iodobenzyl nitrile. The 4-iodobenzyl nitrile was first treated with HCl gas in MeOH to afford conversion to the ester. The mixture was concentrated in vacuo and treated with MeOH (4.7 mL) and chlorotrimethylsilane (10.7 mL) at 50°C for 4h. The reaction was cooled and quenched with H_2O (3.5 mL). Dichloromethane (150 mL) was added followed by Na_2CO_3 (8.9 g) and the mixture was stirred at room temperature for 1h. The organics were separated and dried (Na_2SO_4), filtered, and concentrated to afford 21 g crude (4-iodo-phenyl)-acetic acid methyl ester. ^1H NMR (CDCl_3) δ 7.66 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 3.69 (s, 3H), 3.56 (s, 2H) ppm.

15

Part B. To a THF (100 mL) solution containing sodium hydride (9.5 g, 0.23 mol) at 0°C was added dropwise crude methyl-(4-iodo-phenyl)-acetic acid methyl ester (21 g, 79 mmol, from Part A in THF (50 mL)). After the addition was complete, methyl iodide (11.4 mL, 0.18 mol) in THF (20 mL) was added and the reaction was stirred 72h at rt. The reaction mixture was quenched with ice water followed by extraction with EtOAc. Drying with Na_2SO_4 afforded 27 g of a crude mixture of two products. Purification by chromatography on silica gel (10:1 hexanes/ethyl acetate) afforded 5 g pure methyl 2-(4-iodophenyl)-2-methyl propanoate and 10 g mixture of the desired ester and 2-(4-iodophenyl)-2-methylpropanonitrile. ^1H NMR for methyl 2-(4-iodophenyl)-2-methyl propanoate (CDCl_3) δ 7.65 (d, J = 8.5, 2H), 7.09 (d, J = 8.8 Hz, 2H), 3.64 (s, 3H), 1.54 (s, 6H) ppm.

30

Part C. To 8 g of the crude mixture from Part B in THF (75 mL) and H_2O (25 mL) was added LiOH (3 g), and the reaction

was stirred overnight. Acid/base extraction afforded 3.6 g of 2-(4-iodophenyl)2-methylproprionic acid, Mass Spec (M+H)⁺ 290.8 and 5.3 g of 2-(4-iodophenyl)2-methylproprionitrile. IR(KBr) CN at 2236.66.

5

Part D. To a DMSO (4 mL, degassed) solution of ethyl 1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (0.6 g, 1.9 mmol), and 2-(4-iodophenyl) 2-methylproprionitrile (0.6 g, 2.2 mmol), and K₂CO₃ (0.66 g, 4.8 mmol) and was added CuI (73 mg, 0.3 mmol). The reaction was heated to 130°C for 18h. The reaction was cooled, extracted with EtOAc, washed with H₂O, and dried (MgSO₄). Purification by chromatography on silica gel (1:1 hexanes/ethyl acetate) afforded the title compound 0.4 g (45.9%) of a pale yellow solid; Mass Spec (M+H)⁺ 459.3.

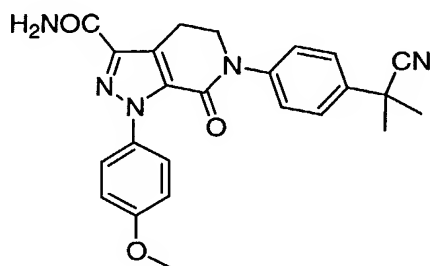
10

15

Example 97

6-[4-(1-cyano-1-methylethyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide

20



Ethyl 6-[4-(cyano-dimethyl-methyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (0.38 g, 0.83 mmol) obtained in Example 96 was placed in a sealed tube containing 10% ammonia in ethylene glycol (3 mL) and heated 80°C for 2h. The reaction was cooled, quenched with H₂O, extracted with EtOAc, and dried (MgSO₄). Recrystallization from

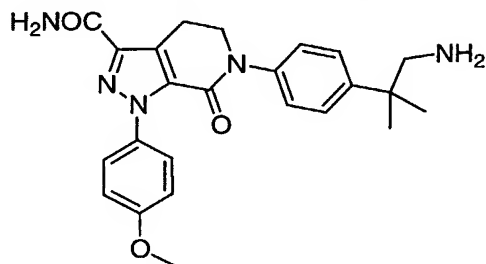
25

30

CH₂Cl₂/Hexanes afforded 0.31g (88%) of the title amide.
 High Resolution Mass Spec (M+H)⁺ for C₂₄H₂₄N₅O₃ 430.1898.

Example 98

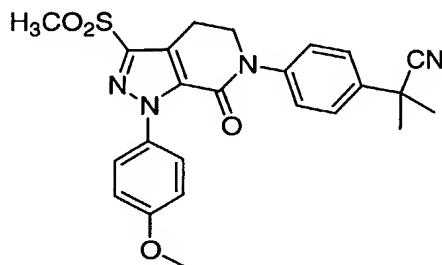
5 **6-[4-(2-Amino-1,1-dimethylethyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide**



10 6-[4-(1-Cyano-1-methylethyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (0.1 g) was hydrogenated at 40psi in EtOH/HCl with 20 mg 10%Pd/C and purified by HPLC to afford 70 mg (56%) of title amine. High Resolution Mass Spec (M+H)⁺ for
 15 C₂₄H₂₈N₅O₃ 434.2176.

Example 99

1-{4-[(1-methoxyphenyl)-3-(methylsulfonyl)-7-oxo-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridinyl-6-yl]phenyl}-2-methylpropanenitrile

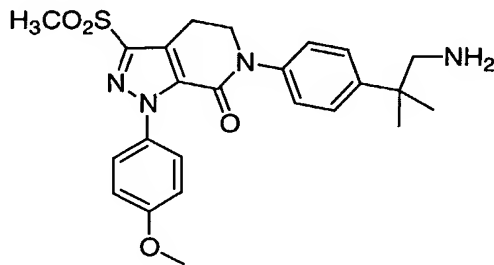


To a degassed DMSO (4 mL) solution containing 1-(4-methoxyphenyl)-3-methylsulfonyl-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (0.6 g, 1.8 mmol) and 2-(4-iodophenyl)-2-methylpropanenitrile (0.6 g, 2.2 mmol) was
 25

added K_2CO_3 (0.64 g, 4.6 mmol) and CuI (71 mg, 0.3 mmol). The reaction was heated to 130°C for 18h. The reaction was cooled, extracted with EtOAc, washed with H_2O , and dried ($MgSO_4$). Purification by chromatography on silica gel (1:1 hexanes/ethyl acetate) afforded 0.52 g (61%) of a pale yellow foam; High Resolution Mass Spec $(M+H)^+$ for $C_{24}H_{25}N_4O_4S$ 456.1624.

Example 100

10 **6-[4-(2-amino-1,1-dimethyl)phenyl]-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one**

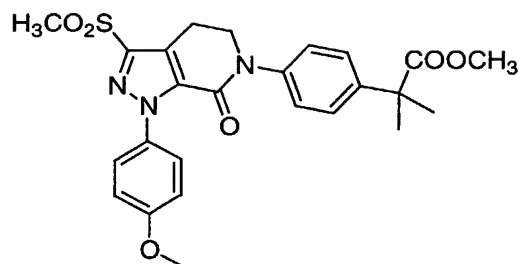


15 1-{1-[(4-Methoxyphenyl)-3-(methylsulfonyl)-7-oxo-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridinyl-6-yl]phenyl}-2-methylpropanenitrile (0.1 g) was hydrogenated at 40psi in EtOH/HCl with 20 mg 10%Pd/C and purified by HPLC to afford 85 mg (68%) of the title amine. High Resolution Mass Spec
20 $(M+H)^+$ for $C_{24}H_{28}N_4O_4S$ 469.1907.

Example 101

Preparation of 2-(4-[3-methanesulfonyl-1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]phenyl)-2-methylproprionic acid methyl ester

25

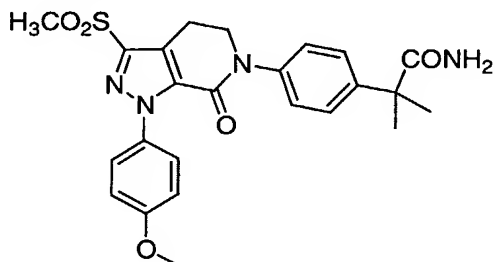


To a degassed DMSO (4 mL) solution was added ethyl 1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (0.4 g, 1.2 mmol) and methyl 2-(4-iodophenyl)-2-methyl propanoate (0.53 g, 1.7 mmol) was added K_2CO_3 (0.43 g, 3.1 mmol) and CuI (47 mg, 0.25 mmol). The reaction was heated to 130°C for 18h, cooled, extracted with EtOAc, washed with H_2O , and dried ($MgSO_4$).

Purification by chromatography on silica gel (1:1 hexanes/ethyl acetate) afforded the titled compound 0.43 g (45.9%) of a pale yellow foam. High Resolution Mass Spec $(M+H)^+$ for $C_{25}H_{28}N_3O_6S$ 498.1691.

Example 102

2-{4-[1-(4-methoxyphenyl)-3-(methanesulfonyl)-7-oxo-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl}-2-methylpropanamide



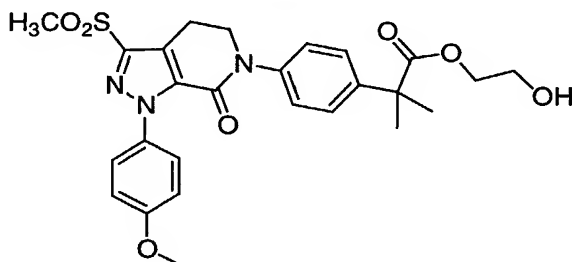
2-{4-[3-Methanesulfonyl-1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]phenyl}-2-methylproprionic acid methyl ester (0.095 g, 0.19 mmol) was placed in a sealed tube containing 10% ammonia in ethylene glycol (3 mL) and heated 80°C for 18h. The reaction was cooled, quenched with H_2O , extracted with EtOAc, and dried

(MgSO₄). Purification by HPLC afforded 35 mg (36%) title compound; High Resolution Mass Spec (M+H)⁺ for C₂₄H₂₇N₄O₅S 483.1725.

5

Example 103

2-Hydroxyethyl-2-(4-[1-(4-methoxyphenyl)-3-(methanesulfonyl)-7-oxo-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridin-6-yl]phenyl)-2-methylpropanoate



10

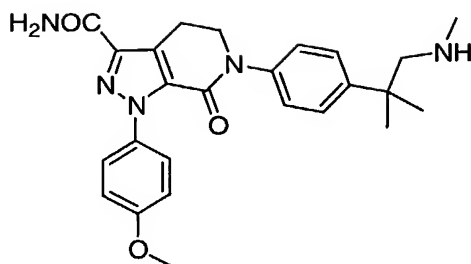
2-(4-[3-Methanesulfonyl-1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]phenyl)-2-methylproprionic acid methyl ester (0.077 g, 0.15 mmol) was placed in a sealed tube containing 10% ammonia in ethylene glycol (3 mL) and heated 80°C for 2h. The reaction was cooled, quenched with H₂O, extracted with EtOAc, and dried (MgSO₄). Purification by chromatography on silica (1:1 hexanes/ethyl acetate) and then HPLC purification afforded 27 mg (33%) title compound. High Resolution Mass Spec (M+H)⁺ for C₂₆H₃₀N₃O₇S 528.1776.

20

Example 104

6-(4-[1,1-dimethyl-2-(methylamino)ethyl]phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide

25



Part A. To ethyl 1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (2.35 g, 7.5 mmol) and 2-(4-iodophenyl)-2-methylproprionic acid (2.6 g, 8.9 mmol) was added K_2CO_3 (3.1 g, 0.022 mol), DMSO (4 mL), and CuI (0.28 mg, 1.4 mmol). The reaction was heated to 130°C for 18h cooled, extracted with EtOAc, washed with H_2O , and dried ($MgSO_4$). Purification by chromatography on silica gel (5%MeOH/ CH_2Cl_2) afforded 1.1 g product.

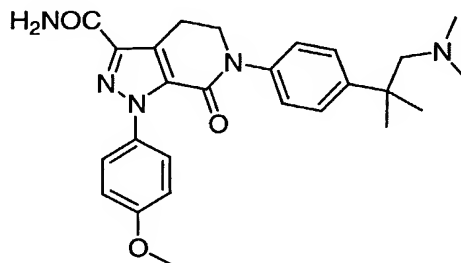
Part B. To the acid from Part A (1 g, 2 mmol) in THF (30 mL) at 0°C was added 1M Borane in THF (2.5 mL, 2.5 mmol) and the reaction was allowed to stir 18h. The reaction was extracted with EtOAc, washed with brine, and dried (Na_2SO_4) to afford crude alcohol. To the alcohol was added CH_2Cl_2 (100 mL), molecular sieves, sodium acetate (0.17 g, 2 mmol), and pyridinium chlorochromate (0.72 g, 3.3 mmol) and the reaction was stirred 24h. After dilution with Et_2O , filtration through paper, and concentration, the crude residue was purified by chromatography on silica gel (2:1 hexanes/EtOAc) to afford 0.527 g of the desired aldehyde.

1H NMR ($CDCl_3$) δ 9.46 (s, 1H), 7.48 (d, J = 9.2 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 9.1 Hz, 2H), 6.92 (d, J = 9.2 Hz, 2H), 4.49 (q, J = 7 Hz, 2H), 4.13 (t, J = 6.6 Hz, 2H), 3.80 (s, 3H), 3.35 (t, J = 6.6 Hz, 2H), 1.45 (t, J = 7.3 Hz, 3H) ppm.

- Part C. To the aldehyde from Part B (95 mg, 0.2 mmol) in 1:1 THF/MeOH (5 mL) was added excess 33% methylamine in EtOH (0.1 mL). After 15 min 0.5M ZnCl₂ in THF (0.2 mL, 0.1 mmol) followed by sodium cyanoborohydride (13 mg, 0.2 mmol) were added. The reaction was stirred 24h. The solvents were removed and the residue was partitioned between EtOAc and H₂O. Extraction with EtOAc and drying (MgSO₄) afforded crude ester/amine.
- Part D. The ester/amine from Part C was heated in a sealed tube containing 2 mL of 10% NH₃/ethylene glycol at 80°C for 2h. After cooling the product was extracted by EtOAc, washed with water and dried (MgSO₄). Purification by HPLC and freeze-drying afforded the titled compound 78 mg (69%) as a white solid. High Resolution Mass Spec (M+H)⁺ for C₂₅H₃₀N₅O₃ 448.2337.

Example 105

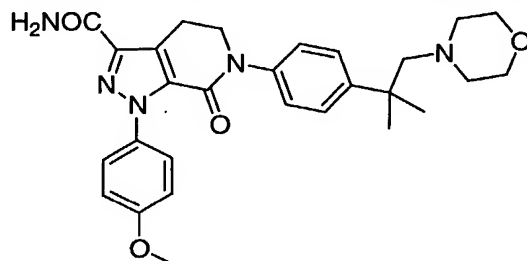
- 6-{4-[2-dimethylethyl]phenyl}-1,1-dimethylethylphenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide



- Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₆H₃₂N₅O₃ 462.2529.

Example 106

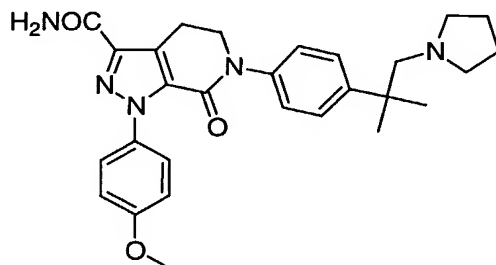
6-{4-[1,1-dimethyl-2-(1-morpholinyl)ethyl]phenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide



5 Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₈H₃₄N₅O₄ 504.2637.

Example 107

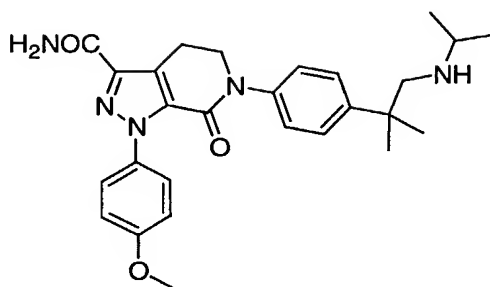
10 6-{4-[1,1-dimethyl-2-(1-pyrrolidinyl)ethyl]phenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide



15 Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₈H₃₄N₅O₃ 488.2667.

Example 108

20 6-{4-[2-(isopropylamino)1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide

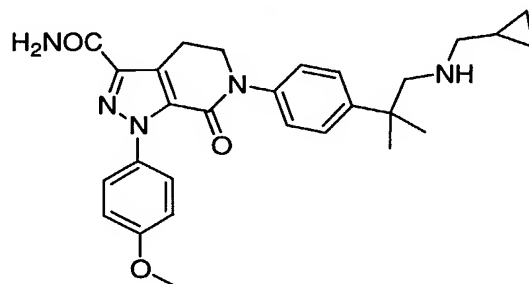


Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₇H₃₄N₅O₃ 476.2666.

5

Example 109

6-(4-{2-[(cyclopropylmethyl)amino]-1,1-dimethylethyl}phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide



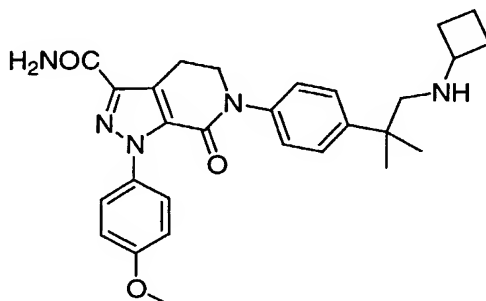
10

Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₈H₃₃N₅O₃ 488.2670.

15

Example 110

6-(4-[2-(cyclobutylamino)-1,1-dimethylethyl]phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide

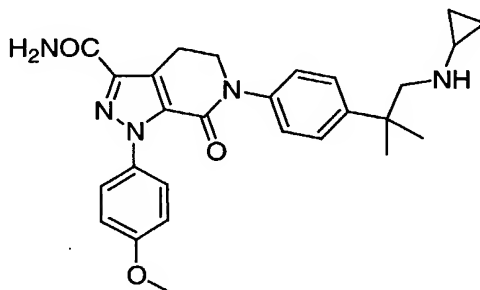


Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₈H₃₄N₅O₃ 488.2668.

5

Example 111

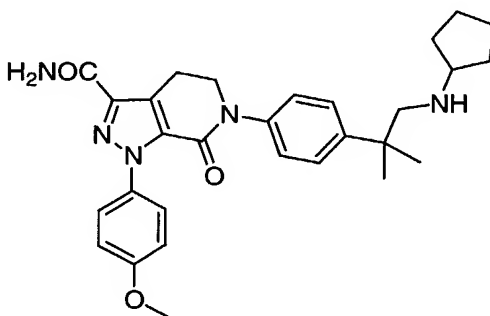
6-{4-[2-(cyclopropylamino)1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide



10 Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₇H₃₂N₅O₃ 474.2513

Example 112

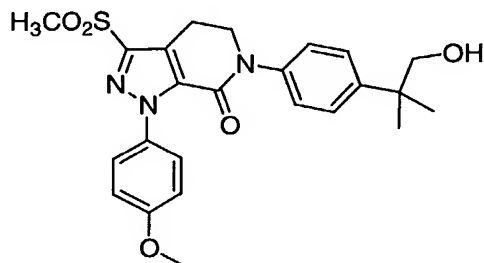
15 **6-{4-[2-(cyclopentylamino)1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide**



20 Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₉H₃₆N₅O₃ 502.2814.

Example 113

6-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-1-(4-methoxyphenyl)-3-(methanesulfonyl)-1,4,5,7-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one



5

Part A. To crude 2-{4-[3-methanesulfonyl-1-(4-methoxyphenyl)-7-oxo-1,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]phenyl}-2-methylproprionic acid methyl ester (2 g, 0.4 mmol) was added LiOH (0.5 g, 12 mmol) in THF/MeOH/H₂O for 24h. The reaction was acidified with 1N HCl and extracted with EtOAc and concentrated to afford crude acid as a semi solid mass.

Part B. The crude acid from Part A was then reduced with 1M borane in THF (7.3 mL, 7.3 mmol) in THF (25 mL) over 24h. The reaction was quenched with water and extracted with EtOAc and dried (MgSO₄) to afford the corresponding alcohol.

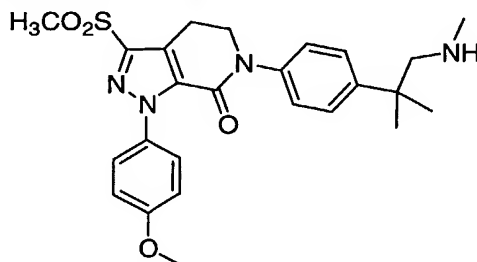
Part C. The crude alcohol from Part B (2.3 g, 4.9 mmol) was oxidized with pyridinium chlorochromate (1.7 g, 7.8 mmol), sodium acetate (0.4 g, 4.9 mmol), and molecular sieves in CH₂Cl₂ for 24h. Dilution with diethyl ether and filtration followed by chromatography on silica gel (1:1 hexanes/EtOAc) afforded 0.6 g (27%) of aldehyde; ¹H NMR CDCl₃ δ 9.46 (s, 1H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.31 (m, 4H), 6.94 (d, *J* = 8.8 Hz, 2H), 4.15 (t, *J* = 6.6 Hz, 2H), 3.81 (s, 3H), 3.36 (t, *J* = 6.6 Hz, 2H), 3.31 (s, 3H), 1.44 (s, 6H) ppm.

30

Part D. To the aldehyde from Part C (34 mg, 0.072 mmol) was added 2-aminoimidazole sulfate (19 mg, 0.144 mmol) in 1:1 THF/MeOH (5 mL) followed by 0.5M ZnCl₂ (0.05 mL, 0.027 mmol) and 1M sodium cyanoborohydride in THF (0.07 mL, 0.07 mmol) and the reaction was stirred 24h. The reaction was quenched with water, extracted with EtOAc, and dried (MgSO₄). Purification by HPLC and freeze-drying afforded 12 mg (35%) of the desired alcohol: ¹H NMR (CDCl₃) δ 7.48 (d, *J* = 9.2 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 9.1 Hz, 2H), 4.15 (t, *J* = 6.6 Hz, 2H), 3.81 (s, 3H), 3.61 (s, 2H), 3.34 (t, *J* = 6.6 Hz, 2H), 3.31 (s, 3H), 1.31 (s, 6H)ppm.

Example 114

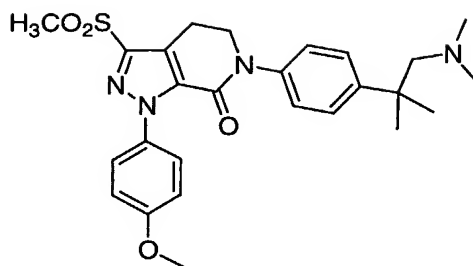
6-{4-[1,1-dimethyl-2-(methylamino)ethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7H-pyrazolo[3,4-*c*]pyridin-7-one



Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₅H₃₁N₄O₄S 483.2049.

Example 115

6-{4-[2-(dimethylamino) 1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7H-pyrazolo[3,4-*c*]pyridin-7-one

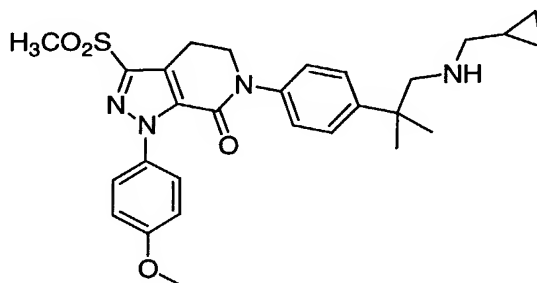


Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₆H₃₃N₄O₄S 497.2201.

5

Example 116

6-(4-(2-[(cyclopropylmethyl)amino]-1,1-dimethylethyl)phenyl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one



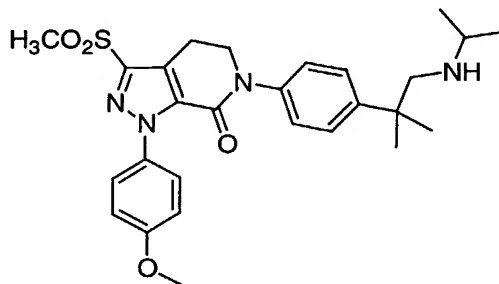
10

Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₈H₃₅N₄O₄S 523.2362.

15

Example 117

6-(4-[1,1-dimethyl-2-(isopropylamino)ethyl]phenyl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one

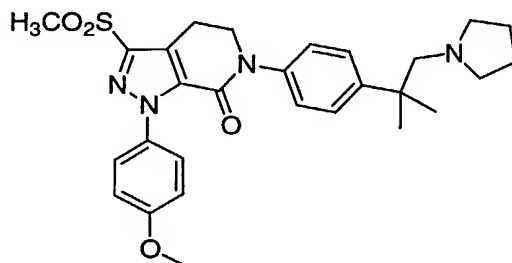


Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₇H₃₅N₄O₄S 511.2379.

5

Example 118

6-{4-[1,1-dimethyl-2-(1-pyrrolidinyl)ethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one

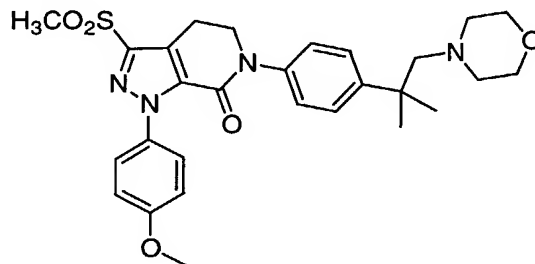


10 Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₈H₃₅N₄O₄S 523.2388.

15

Example 119

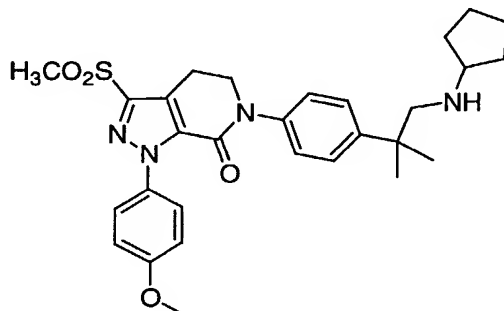
6-{4-[1,1-dimethyl-2-(1-morpholinyl)ethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one



20 Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₈H₃₅N₄O₅S 539.2342.

Example 120

6-{4-[2-(cyclopentylamino) 1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one



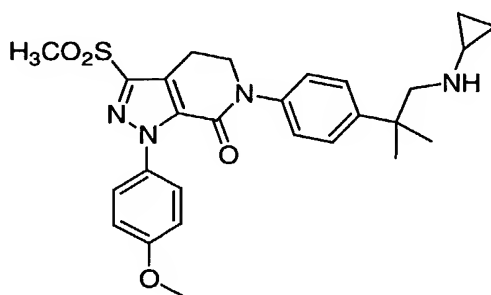
5

Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₉H₃₇N₄O₄S 537.2539.

10

Example 121

6-(4-{2-((cyclopropylamino) 1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one



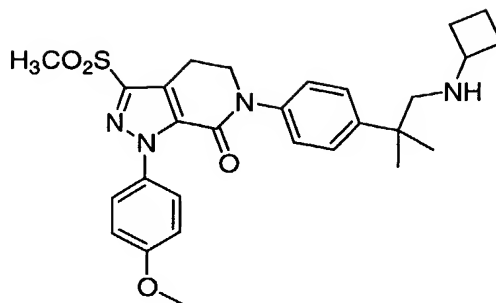
15

Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₇H₃₃N₄O₄S 509.2227.

20

Example 122

6-{4-[2-(cyclobutylamino) 1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,7-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one

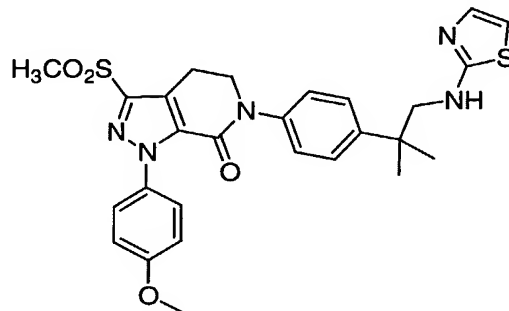


Following a procedure analogous to that used in Example 104, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₈H₃₅N₄O₄S 523.238.

5

Example 123

6-{4-[1,1-dimethyl-2-(1,3-thiazol-2-yl amino)ethyl]phenyl}-1-(4-methoxyphenyl)-3-(methanesulfonyl)-1,4,5,7-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one

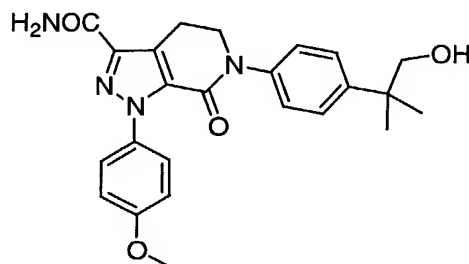


10

Prepared as previously described above. High Resolution Mass Spec (M+H)⁺ for C₂₇H₃₀N₅O₄S₂ 552.1727.

Example 124

6-[4-(2-hydroxy-1,1-dimethylethyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide

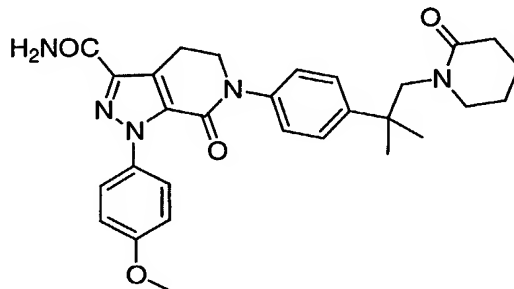


Following a procedure analogous to that used in Example 113, the title compound was prepared. High Resolution Mass Spec (M+H)⁺ for C₂₄H₂₇N₄O₄ 435.2016.

5

Example 125

6-{4-[1,1-dimethyl-2-(2-oxo-1-piperidinyl)ethyl]phenyl}-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide



10

To 6-[4-(1-cyano-1-methylethyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (0.17 g, 0.39 mmol) was hydrogenated at 40psi in ethanol with 0.5 mL conc. HCl and 10% palladium on carbon (25 mg) for 72h. The reaction was filtered and concentrated. To the amine in THF (5 mL) at 0°C was added 5-bromovaleryl chloride (99 mg, 0.5 mmol) and TEA (1 mL) and the reaction was stirred 1h. To the reaction was added potassium *t*-butoxide (0.24 g, 1.9 mmol) and the reaction was stirred 24h. The reaction was quenched with water and extracted with ethyl acetate and dried (MgSO₄). Purification by HPLC and freeze-drying afforded 15 mg (7.5%). Mass Spec (M+H)⁺ 516.3.

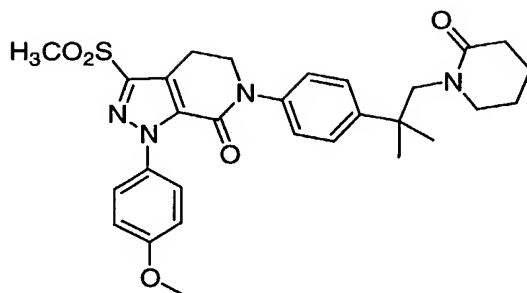
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Example 126

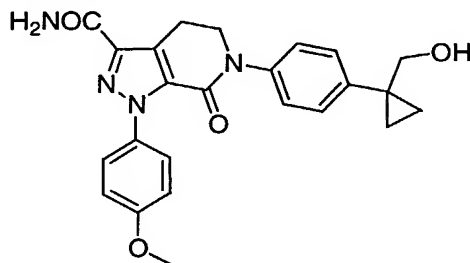
6-{4-[1,1-dimethyl-2-(2-oxo-1-piperidinyl)ethyl]phenyl}-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one



1-{4-[(1-Methoxyphenyl)-3-(methanesulfonyl)-7-oxo-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridinyl-6-yl]phenyl}-2-methylpropanenitrile was converted into the
 5 target compound by the same procedure as that of Example 125. Mass Spec (M+H)⁺ 551.3.

Example 127

10 **6-[4-(1-Hydroxymethylcyclopropyl)phenyl]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide**

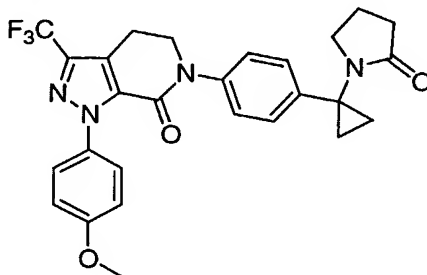


Following a procedure analogous to that used in Example 95, the title compound was prepared. LC/MS (ESI⁺) 433.4 (M+H)⁺.

15

Example 128

1-(4-Methoxyphenyl)-6-{4-[1-(2-oxo-pyrrolidin-1-yl)-cyclopropyl]phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one



20

Part A. 4-Iodophenylcyclopropyl carboxylic acid (7.42 g, 25.76 mmol) was stirred in CH_2Cl_2 (60 mL) at rt under N_2 . Et_3N (5.4 mL, 38.64 mmol, 1.5 eq) was added followed by the addition of DPPA (8.27 mL, 38.64 mmol, 1.5 eq). The resulting mixture was stirred at rt overnight. It was poured into ice H_2O (100 mL), acidified with 6N HCl , and then extracted with CH_2Cl_2 . The organic layer was washed with H_2O and brine, dried over MgSO_4 , filtered, and concentrated under vacuum. The oil residue obtained was dissolved in *t*-BuOH (40 mL) and refluxed for 2-3 h. After cooling, the solvent was evaporated. The residue was purified by FCC (silica gel, hexane: CH_2Cl_2 =1:1, then CH_2Cl_2 , then CH_2Cl_2 :MeOH=100:1 to 25:1) to give pure [1-(4-iodophenyl)-cyclopropyl]-carbamic acid *tert*-butyl ester (6.01 g, yield: 65%). This compound (2.12 g, 5.89 mmol) was stirred in CH_2Cl_2 (10 mL) and TFA (10 mL) at rt for 2h. After evaluation, the residue was taken up in CHCl_3 (100 mL) and H_2O (100 mL). The aqueous layer was basified with K_2CO_3 , extracted with CHCl_3 (2 x), dried over MgSO_4 , filtered, and concentrated to dryness to give pure 1-(4-iodophenyl)cyclopropylamine (1.50 g, yield: 98%). ^1H NMR (CDCl_3) δ 7.62 (m, 2H), 7.06 (m, 2H), 1.88 (m, 2H), 1.07 (m, 2H), 0.95 (m, 2H) ppm. HRMS $\text{C}_9\text{H}_{11}\text{IN}$ ($\text{M}+\text{H}$) $^+$ 259.9930 calcd for 259.9936.

25

Part B. The mixture of the product from Part A (0.32 g, 1.24 mmol), NaOH (0.15 g, 3.72 mmol, 3.0 eq), and 4-chlorobutyryl chloride (0.18 mL, 1.61 mmol, 1.3 eq) was stirred in CH_2Cl_2 (7 mL) at rt for 1 h under N_2 . H_2O was added. It was extracted with EtOAc (2x), washed with H_2O and brine, dried over MgSO_4 , and concentrated to dryness. The residue was dissolved in THF (10 mL). KOtBu (0.40 g, 4.16 mmol) was added as one portion. The mixture was

30

stirred at 0°C under N₂ for 30 min. EtOAc was added. It was washed with H₂O and brine, dried over MgSO₄, and concentrated to produce 1-[1-(4-iodophenyl)cyclopropyl]-pyrrolidin-2-one (0.27 g, yield: 100%). ¹H NMR (CDCl₃) δ

5 7.68 (d, *J*=8.5 Hz, 2H), 6.87 (d, *J*=8.5 Hz, 2H), 3.26 (t, *J*=7.3 Hz, 2H), 2.26 (t, *J*=7.6 Hz, 2H) 1.88 (t, *J*=7.0 Hz, 2H), 1.22 (m, 2H), 1.10 (m, 2H) ppm.

Part C. The product from Part B (64 mg, 0.196 mmol) and 1-

10 (4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (0.061 g, 0.196 mmol) were stirred in DMSO (0.3 mL) under N₂. K₂CO₃ (0.067 g, 0.49 mmol, 2.5 eq) was added, followed by the addition of CuI (0.037 g, 0.194 mmol) and 1,10-phenanthroline (0.020 g,

15 0.108 mmol). The resulting mixture was heated at 120°C for 3h. After cooling, it was extracted with EtOAc (2x), washed with H₂O and brine, dried over MgSO₄, filtered, and concentrated to dryness. The residue was purified by FCC (silica gel, CH₂Cl₂:EtOAc=1:1, then EtOAc) to give 1-(4-

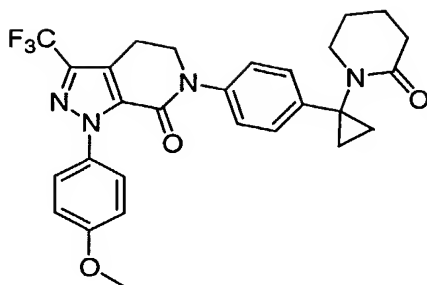
20 methoxyphenyl)-6-{4-[1-(2-oxo-pyrrolidin-1-yl)-cyclopropyl]phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one (45 mg, yield: 45%). ¹H NMR (CDCl₃) δ 7.46 (d, *J*=8.8 Hz, 2H), 7.25 (AA'BB', *J*=8.6 Hz, 4H), 6.91 (d, *J*=9.2 Hz, 2H), 4.10 (t, *J*=6.6 Hz, 2H), 3.81

25 (s, 3H), 3.38 (t, *J*=7.2 Hz, 2H), 3.14 (t, *J*=6.6 Hz, 2H), 2.37 (t, *J*=7.7 Hz, 2H), 1.98 (q, *J*=7.7 Hz, 2H), 1.32 (m, 2H), 1.21 (m, 2H) ppm. HRMS C₂₇H₂₆F₃N₃O₄ (M+H)⁺ 511.1931 calcd for 511.1958.

30

Example 129

1-(4-Methoxyphenyl)-6-{4-[1-(2-oxo-piperidin-1-yl)-cyclopropyl]phenyl}-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one



Following the procedures analogous to those used in Example 128, the title compound was prepared. The product was purified by RP-prep LC-MS (35-98% CH₃CN/H₂O in a 10-min

5 run). HRMS C₂₉H₃₂O₂F₃N₄ (M+H)⁺ 525.2486 calcd for 525.2477.

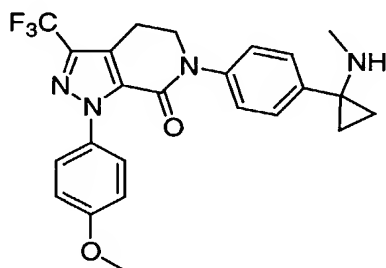
¹H NMR (CDCl₃) δ 7.46 (d, J=8.8 Hz, 2H), 7.25 (d, J=8.4 Hz, 2H), 6.91 (d, J=9.2 Hz, 2H), 4.10 (t, J=6.6 Hz, 2H), 3.82 (s, 3H), 3.37 (t, J=6 Hz, 2H), 3.15 (t, J=6.6 Hz, 2H), 2.51 (t, J=6 Hz, 2H), 1.79 (m, 4H), 1.33 (m, 2H), 1.29 (m, 2H)

10 ppm.

Example 130

1-(4-Methoxyphenyl)-6-[4-(1-methylaminocyclopropyl)-phenyl]-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one

15



Part A. 1-(4-Iodophenyl)cyclopropyl-carbamic acid tert-butyl ester (2.14 g, 5.85 mmol) was stirred in THF (20 mL) at 0°C under N₂. MeI (3 mL) was added followed by

20 portionwise addition of NaH (2.34 g, 5 eq). The reaction was stirred at rt overnight. Several drops of H₂O and EtOAc (20 mL) were added to quench the reaction. The organic solvent was evaporated, and H₂O was added. It was extracted with Et₂O (2x), washed with brine, dried over

MgSO₄, and concentrated to dryness. The residue was purified by FCC (silica gel, CH₂Cl₂:hexanes=0:1 to 1:1 to 1:0) to give pure [1-(4-iodophenyl)cyclopropyl]-methyl-carbamic acid *tert*-butyl ester as a white solid (2.07 g, 5 yield 95%). LC/MS (ESI⁺) 373.8 (M+H), t_R=2.95 min (10-90% CH₃CN in H₂O in a 4-min run).

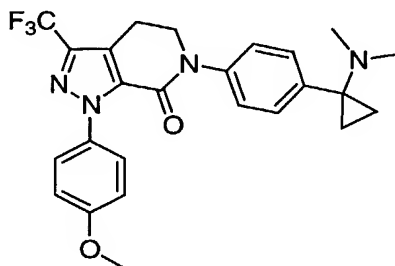
Part B. The product from Part A (205 mg, 0.55 mmol) and 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-10 7*H*-pyrazolo[3,4-*c*]pyridin-7-one (170 mg, 0.55 mmol) were stirred in DMSO (0.4 mL) under N₂. K₂CO₃ (250 mg, 1.81 mmol, 3.3 eq) was added, followed by the addition of CuI (52 mg, 0.27 mmol, 0.5 eq) and 1,10-phenanthroline (50 mg, 0.27 mmol, 0.5 eq). The resulting mixture was heated at 15 120°C for 2h. After cooling, it was extracted with EtOAc (2x), washed with H₂O and brine, dried over MgSO₄, filtered, and concentrated to dryness. The residue was purified by flash column chromatography (silica gel, CH₂Cl₂:EtOAc=1:1, then EtOAc) to give (1-{4-[1-(4-methoxyphenyl)-7-oxo-3-20 trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropyl)-methyl-carbamic acid *tert*-butyl ester (250 mg, yield: 82%). ¹H NMR (CDCl₃) δ 7.46 (d, *J*=9.2 Hz, 2H), 7.23 (d, *J*=8.4 Hz, 2H), 7.09 (m, 2H), 6.91 (d, *J*=9.1 Hz, 2H), 4.12 (t, *J*=6.6 Hz, 2H), 3.81 (s, 3H), 3.15 25 (t, *J*=6.6 Hz, 2H), 2.90 (s, br, 3H), 1.42 (s, br, 9H), 1.33 (m, 2H), 1.20 (m, 2H) ppm. LC/MS (ESI⁺) 557.4.

Part C. The product from Part B (250 mg, 0.45 mmol) was stirred in CH₂Cl₂ (2 mL) and TFA (2 mL) at rt for 20 min. 30 The solvents were evaporated. The residue was purified by FCC (silica gel, EtOAc, then EtOAc: MeOH=10:1) to yield the title compound (188 mg, 92%). ¹H NMR (CDCl₃) δ 7.55 (d, *J*=8.4 Hz, 2H), 7.45 (d, *J*=9.2 Hz, 4H), 7.36 (d, *J*=8.4 Hz, 2H), 6.91 (d, *J*=8.8 Hz, 2H), 4.15 (t, *J*=6.6 Hz, 2H), 3.80

(s, 3H), 3.17 (t, $J=6.6$ Hz, 2H), 2.50 (s, 3H), 1.56 (m, 2H), 1.12 (m, 2H) ppm. LC/MS (ESI⁺) 457.4.

Example 131

5 **6-[4-(1-Dimethylaminocyclopropyl)phenyl]-1-(4-methoxyphenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-*c*]pyridin-7-one**

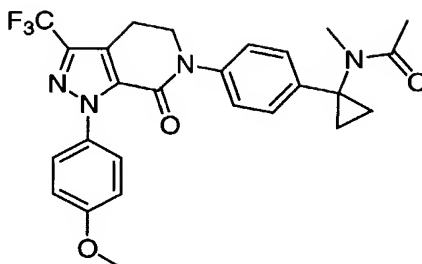


The product from Example 130 (30 mg, 0.066 mmol) was
10 stirred in CH₃CN (0.2 mL) at rt under N₂. Aqueous
formaldehyde (0.07 mL, 7 mmol, 10 eq) was added followed by
the addition of HOAc (0.012 mL, 0.21 mmol, 3.2 eq). The
mixture was stirred for 15 min, and then NaBH₃CN (12 mg,
0.198 mmol) was added. The mixture was stirred at rt for
15 2h. Several drops of acetone were added followed by 1N
NaOH. The mixture was extracted with CH₂Cl₂, washed with
H₂O and brine, dried over MgSO₄, and concentrated to
dryness. The residue was purified by FCC (silica gel,
EtOAc, then EtOAc: MeOH=10:1) to yield the title compound
20 (15.7 mg, 51%). ¹H NMR (CDCl₃) δ 7.46 (d, $J=8.8$ Hz, 2H),
7.29 (m, 4H), 6.92 (d, $J=9.2$ Hz, 2H), 4.15 (t, $J=6.6$ Hz,
2H), 3.81 (s, 3H), 3.16 (t, $J=6.6$ Hz, 2H), 2.28 (s, 6H),
1.02 (m, 2H), 0.81 (m, 2H) ppm. LC/MS (ESI⁺) 471.4.

25

Example 132

***N*-(1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-cyclopropyl)-*N*-methyl-acetamide**

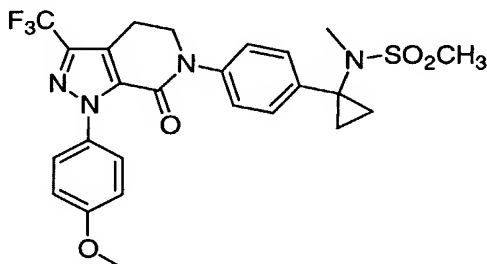


Following a procedure analogous to that used for the preparation of Example 93, the title compound was prepared. Silica gel purification yielded the title compound. LC/MS
 5 (ESI⁺) 499.4 (M+H). ¹H NMR (CDCl₃) δ 7.46 (d, J=9.2 Hz, 2H), 7.26 (m, 2H), 6.93 (AA'BB', J=8.8, 7.0 Hz, 4H), 4.12 (t, J=6.6 Hz, 2H), 3.81 (s, 3H), 3.16 (t, J=6.6 Hz, 2H), 3.01 (s, 3H), 2.05 (s, 3H), 1.50 (m, 4H) ppm.

10

Example 133

***N*-(1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-cyclopropyl)-*N*-methyl-methanesulfonamide**

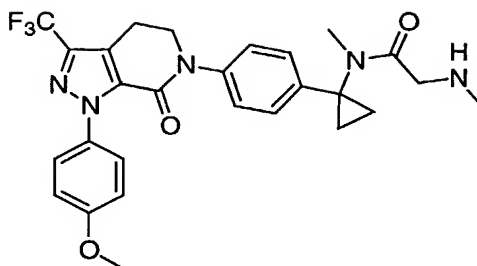


15 Following a procedure analogous to that used for the preparation of Example 94, the title compound was prepared. Silica gel purification yielded the pure desired product. LC/MS (ESI⁺) 535.6 (M+H)⁺.

20

Example 134

***N*-(1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-cyclopropyl)-*N*-methyl-2-methylaminoacetamide**

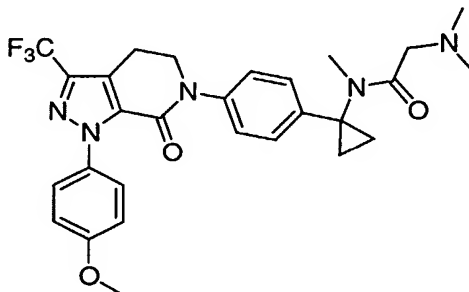


Part A. The product of Example 130 (45 mg, 0.1 mmol) was stirred in CH_2Cl_2 (1 mL) at rt. NaOH (12 mg, 3.0 eq) was added followed by the addition of chloroacetyl chloride
 5 (0.015 mL, 2.0 eq). The mixture was stirred at rt for 3h. Additional NaOH (20 mg) and chloroacetyl chloride (0.020 mL) were added. The mixture was stirred at rt overnight. The mixture was extracted with CH_2Cl_2 (2x), washed with H_2O and brine, dried over MgSO_4 , filtered, and concentrated to
 10 dryness. The residue was used directly in the next step without further purification. LC/MS (ESI⁺) 533.6 (M+H), t_R =2.63 min (10-90% CH_3CN in H_2O in a 4-min run).

Part B. The product from part A (15 mg, 0.028 mmol) was
 15 stirred in DMF (0.1 mL) in a Pyrex tube under N_2 . K_2CO_3 (20 mg) was added, followed by the addition of a solution of NHMe_2 in THF (2M, 0.1 mL). The reaction mixture was stirred at 80°C overnight. H_2O was added, and the mixture was extracted with EtOAc, washed with brine, dried over
 20 MgSO_4 , filtered, and concentrated. The residue was purified by FCC (silica gel, CH_2Cl_2 , then CH_2Cl_2 :EtOAc, then EtOAc:MeOH=10:1) to give the title compound (5.0 mg, yield: 33%). ^1H NMR (CDCl_3) δ 7.46 (d, J =8.8 Hz, 2H), 7.29 (m, 4H), 6.92 (d, J =9.2 Hz, 2H), 4.15 (t, J =6.6 Hz, 2H), 3.81
 25 (s, 3H), 3.16 (t, J =6.6 Hz, 2H), 2.28 (s, 6H), 1.02 (m, 2H), 0.81 (m, 2H) ppm. LC/MS (ESI⁺) 528.6 (M+H), t_R =2.07 min (10-90% CH_3CN in H_2O in a 4-min run).

Example 135

2-Dimethylamino-N-(1-{4-[1-(4-methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]phenyl}cyclopropyl)-N-methylacetamide



5

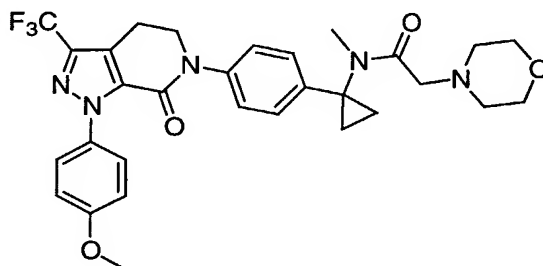
Following a procedure analogous to that used for the preparation of Example 134, the title compound was prepared. Silica gel purification yielded the pure desired product. LC/MS (ESI⁺) 542.6 (M+H), *t_R*=2.10 min (10-90% CH₃CN in H₂O in a 4-min run).

10

Example 136

N-(1-{4-[1-(4-Methoxyphenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]phenyl}-cyclopropyl)-N-methyl-2-morpholin-4-yl-acetamide

15

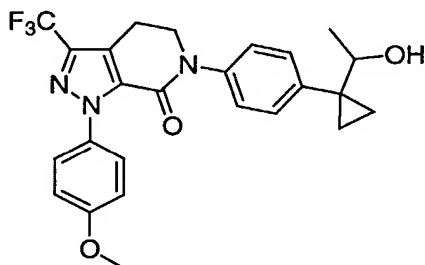


Following a procedure analogous to that used for the preparation of Example 134, the title compound was prepared. Silica gel purification yielded the pure desired product. LC/MS (ESI⁺) 584.2 (M+H)⁺, *t_R*=2.05 min (10-90% CH₃CN/H₂O in a 4-min run).

20

Example 137

6-{4-[1-(1-Hydroxyethyl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one



5

1-{4-[1-(4-Methoxy-phenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]-phenyl}-

cyclopropanecarbaldehyde (93 mg, 0.21 mmol) was stirred in Et₂O (2 mL) at -78°C. ZnMe₂ (2M in toluene, 0.16 mL, 1.5

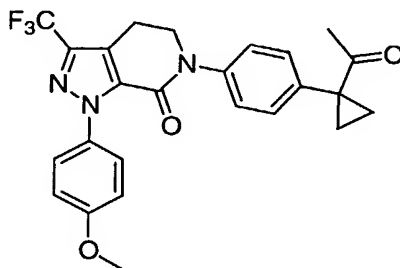
10 eq) was added followed by the addition of TiCl₄ (1 M in CH₂Cl₂, 0.3 mL). The resulting mixture was stirred for 1h.

The reaction was quenched by addition of NH₄Cl, extracted with EtOAc, washed with H₂O and brine, dried over MgSO₄, filter, and concentrated. The residue was purified by

15 silica gel column to yield the pure desired product (62 mg, yield: 64.5%). LC/MS (ESI⁺) 472.6 (M+H)⁺, t_R=2.44 min (35-95% CH₃CN/H₂O in a 6-min run).

Example 138

20 **6-[4-(1-Acetylcyclopropyl)phenyl]-1-(4-methoxyphenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one**

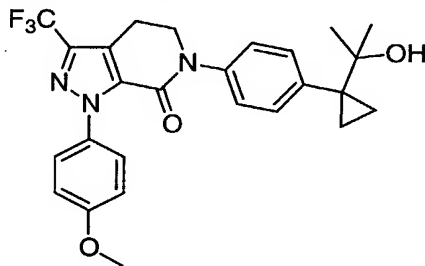


The product from Example 137 (30 mg, 0.063 mmol) was
25 stirred in CH₂Cl₂ (1 mL) at rt under N₂. 4Å molecular sieves

(30 mg) and NaOAc (15.4 mg, 0.187 mmol) were added followed by the addition of PCC (27.5 mg, 0.126 mmol). The reaction mixture was stirred at rt for 1.5 h. The mixture was filtered through Celite®, rinsed with CH₂Cl₂, washed with H₂O, brine, concentrated to dryness. Silica gel purification afforded the title compound. LC/MS(ESI⁺) 470.6 (M+H)⁺, t_R=2.77 min (10-90% CH₃CN/H₂O in a 4-min run). ¹H NMR (CDCl₃) δ 7.47 (d, J=8.4 Hz, 2H), 7.33 (AA'BB', J=8.8 Hz, 4H), 6.93 (dd, J=8.8, 2.3 Hz, 2H), 4.16 (t, J=6.6 Hz, 2H), 3.83 (s, 3H), 3.29 (t, J=6.6 Hz, 2H), 2.77 (s, 6H), 1.67 (m, 2H), 1.15 (m, 2H) ppm.

Example 139

6-{4-[1-(1-Hydroxy-1-methyl-ethyl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-trifluoromethyl-1,4,5,6-tetrahydropyrazolo[3,4-c]pyridin-7-one



Part A. 1-(4-Iodo-phenyl)-cyclopropanecarboxylic acid methyl ester (0.96 g, 3.17 mmol) was stirred in THF (15 mL) at -78°C under N₂. MeMgCl (3.0 M in THF, 4.2 mL, 4.0 eq) was added dropwise, and the reaction was stirred for 1 h during which period the temperature was raised from -78°C to 0°C. It was quenched by the addition of sat'd NH₄Cl, and extracted with EtOAc (2 x). The organics were washed with H₂O and brine, dried over MgSO₄, filtered, and concentrated to dryness. The residue was purified by FCC (silica gel, hexanes, then hexanes:CH₂Cl₂=1:1 to 0:1) to give 2-[1-(4-iodo-phenyl)-cyclopropyl]-propan-2-ol (0.71 g,

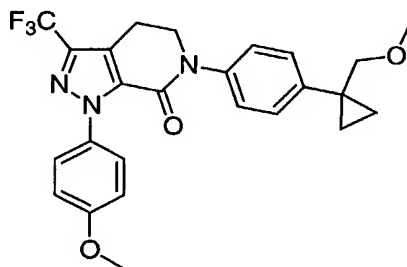
yield: 73.9%). LC/MS(ESI⁺) 303.4 (M+H)⁺, t_R=2.57 min (10-90% CH₃CN/H₂O in a 4-min run).

Part B. The product from Part A (102 mg, 0.33 mmol) and
5 (105 mg, 0.34 mmol) were stirred in dry DMSO (0.5 mL).
K₂CO₃ (90.5 mg, 2.0 eq) was added followed by the addition
of CuI (32 mg, 0.17 mmol) and 1,10-phenanthroline (31 mg,
0.17 mmol). The resulting mixture was heated at 120°C for
3h. After cooling, it was extracted with EtOAc (2x),
10 washed with H₂O and brine, dried over MgSO₄, filtered, and
concentrated to dryness. The residue was purified by FCC
(silica gel, CH₂Cl₂:EtOAc=1:1, then EtOAc) to give the title
compound (95 mg, yield: 59.4%). LC/MS(ESI⁺) 486.8 (M+H)⁺,
t_R=3.03 min (10-90% CH₃CN/H₂O in a 4-min run).

15

Example 140

6-[4-(1-Methoxymethylcyclopropyl)phenyl]-1-(4-methoxyphenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one



20

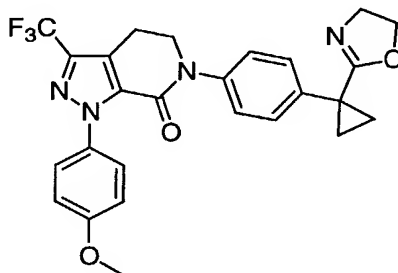
Part A. [1-(4-Iodo-phenyl)-cyclopropyl]-methanol (0.25 g, 0.94 mmol) was dissolved in CH₂Cl₂ (1.5 mL). Proton sponge (0.21 g, 0.97 mmol) was added followed by trimethoxyloxonium tetrafluoroborate (0.15 g, 1.0 mmol).
25 The reaction was allowed to stir for 3 h and was then quenched with H₂O, concentrated, and purified via flash chromatography (silica, 100% EtOAc) to afford the title compound (0.13 g, yield: 47%). ¹H NMR (CDCl₃) δ 7.64 (d, J=8.4 Hz, 2H), 7.11 (d, J=8.2 Hz, 2H), 3.65 (d, J=6.2 Hz, 2H), 1.57 (s, 3H), 0.86 (s, 4H) ppm.

30

Part B. The product from Part A and 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one were coupled using the usual Buchwald Ullman procedure. LC/MS (ESI⁺) 472.6 (M+H)⁺, t_R=2.98 min (10-90% CH₃CN/H₂O in a 4-min run). ¹H NMR ((CD₃)₂CO, 300 MHz) δ 7.49 (d, J=9.1 Hz, 2H), 7.29 (AA'BB', J=8.8 Hz, 4H), 6.96 (dd, J=9.2 Hz, 2H), 4.15 (t, J=6.6 Hz, 2H), 3.82 (s, 3H), 3.44 (s, 2H), 3.23 (s, 3H), 3.16 (t, J=6.3 Hz, 2H), 0.84 (d, J=2.2 Hz, 2H), 0.81 (d, J=2.5 Hz, 2H) ppm.

Example 141

6-{4-[1-(4,5-Dihydro-oxazol-2-yl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-trifluoromethyl-1,4,5,6-tetrahydro-pyrazolo[3,4-c]pyridin-7-one



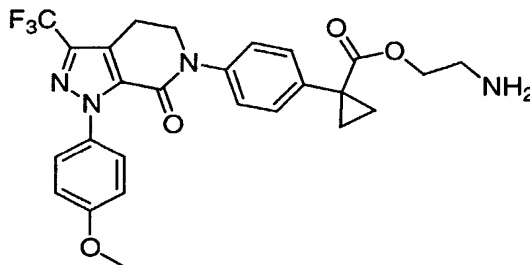
Part A. To a slurry of 1-(4-iodo-phenyl)-cyclopropanecarboxylic acid (0.693 g, 2.41 mmol) in CH₂Cl₂ (3.0 mL) at 0°C was added (COCl)₂ (0.40 mL, 4.6 mmol) dropwise. The reaction was warmed to rt and stirred under N₂ for 1 h. The reaction was monitored by LC/MS. Upon completion the reaction was concentrated on the rotary evaporator and diluted with CH₂Cl₂ (3 mL). Ethanolamine (0.30 mL, 4.54 mmol) was added drop-wise and the reaction stirred for 1.5 h. The reaction was then quenched with H₂O and extracted with EtOAc (2x). The organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated to dryness. The crude 1-(4-iodo-phenyl)-cyclopropanecarboxylic acid (2-hydroxy-ethyl)-amide was

taken directly to the next reaction without further purification. LC/MS (ESI+) 332.2 (M+H)⁺, t_R=2.16 min (10-90% CH₃CN/H₂O in a 4-min run). It was dissolved in THF (10.0 mL) and methoxycarbonylsulfamoyl triethylammonium hydroxide inner salt (0.61 g, 2.56 mmol) was added. The reaction was heated to 70°C for 2h and then cooled. The reaction mixture was diluted with EtOAc and washed with H₂O (2x), brine, dried over Na₂SO₄, filtered, and concentrated to dryness. The residue was purified by flash chromatography (silica, EtOAc: Hexanes 3:1) to 2-[1-(4-iodo-phenyl)-cyclopropyl]-4,5-dihydro-oxazole (0.41 g, yield: 55%). LC/MS (ESI+) 314.0 (M+H), t_R=1.62 min (10-90% CH₃CN/H₂O in a 4-min run). ¹H NMR (CDCl₃) δ 7.65 (d, J=8 Hz, 2H), 7.13 (d, J=8.4 Hz, 2H), 4.32 (t, J=9.5 Hz, 2H), 3.87 (t, J=9.1, 9.6, 2H), 1.67 (m, 2H), 1.23 (m, 2H) ppm.

Part B. The product from Part A (75.2 mg, 0.240 mmol) and 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one (76.8 mg, 0.247 mmol) were dissolved in DMSO (0.5 mL). Potassium carbonate (0.109 g, 0.788 mmol), copper iodide (spatula tip), and 1,10-phenanthroline (spatula tip) were added and the reaction was heated to 120°C for 12h under an environment of N₂. The reaction was cooled, diluted with EtOAc, washed with H₂O (2x), brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 100% EtOAc) afforded the title compound. LC/MS (ESI+) 497.6 (M+H), t_R=2.44 min (10-90% CH₃CN/H₂O in a 4-min run). ¹H NMR ((CD₃)₂CO, 300 MHz) δ 7.51 (d, J=9.0 Hz, 2H), 7.32 (AA'BB', J=8.4 Hz, 4H), 6.97 (d, J=9.0 Hz, 2H), 4.16 (m, 4H), 3.82 (s, 3H), 3.67 (t, J=9.2 Hz, 2H), 3.17 (t, J=6.6 Hz, 2H), 2.02 (m, 2H), 1.42 (m, 2H), 1.17 (m, 2H) ppm.

Example 142

1-{4-[1-(4-Methoxy-phenyl)-7-oxo-3-trifluoromethyl-1,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]-phenyl}-cyclopropanecarboxylic acid 2-amino-ethyl ester



5

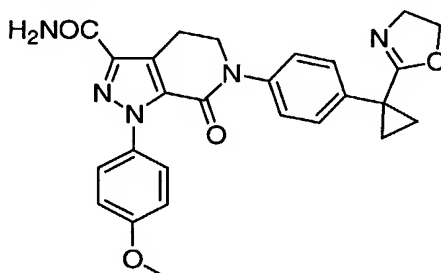
A side product resulting from a minor impurity in the starting material of Part C of Example 141 was isolated and characterized to be the title compound. LC/MS (ESI⁺) 515.6 (M+H)⁺, t_R=2.22 min (10-90% CH₃CN/H₂O in a 4-min run). ¹H

10 NMR (CD₃)₂CO, δ 7.50 (d, J=8.8 Hz, 2H), 7.38 (AA'BB', J=8.6 Hz, 4H), 7.00 (d, J=8.8 Hz, 2H), 4.20, (t, 2H), 3.83 (s, 3H), 3.45 (t, 2H), 3.20 (m, 4H), 1.40 (m, 2H), 0.95 (m, 2H) ppm.

15

Example 143

6-{4-[1-(4,5-Dihydro-oxazol-2-yl)-cyclopropyl]-phenyl}-1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide



20 Part A. The product of Part A from Example 141 (0.10 g, 0.32 mmol) and 1-(4-methoxy-phenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid ethyl ester (0.10 g, 0.32 mmol) were dissolved in DMSO (1.5 mL). Potassium carbonate (1.3 g, 0.94 mmol), copper iodide
25 (0.02 g, 0.10 mmol), and 1,10-phenanthroline (0.02 g, 0.11